National Clinical Guideline Centre

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Draft for consultation

NAFLD

Assessment and management of non-alcoholic fatty liver disease (NAFLD) in adults, children and young people

NICE guideline

Appendices A – R

December 2015

Draft for consultation

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians

The Royal College of Surgeons of England

RCGP Royal College of General Practitioners

Royal College of Nursing

NICE accredited

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Funding
National Institute for Health and Care Excellence

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Appendices

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

1 Guideline title

Liver disease (non-alcoholic fatty): assessment and management of non-alcoholic fatty liver disease (NAFLD) in adults, children and young people

1.1 Short title

Liver disease (non-alcoholic fatty [NAFLD])

2 The remit

The Department of Health has asked NICE: 'to develop a clinical guideline on the management of liver disease (non-alcoholic)'.

3 Need for the guideline

3.1 Epidemiology

a) Primary non-alcoholic fatty liver disease (NAFLD) is a term used to describe excess fat in the liver (steatosis) in the absence of excessive alcohol consumption or any of the other secondary causes of steatosis. These include the side-effects of certain medications, hepatitis C virus infection and particular endocrine conditions. NAFLD is more common in certain ethnic groups including people of Latin American and South Asian family origin.

b) The severity of NAFLD ranges from simple steatosis, to fat with inflammation and fibrosis (non-alcoholic steatohepatitis [NASH]), to cirrhosis.

c) The prevalence of NAFLD in the general population is estimated at 20–30%; this figure is based largely on ultrasound studies in other similar populations. NASH is present in around 2–3% of the

Liver disease (non-alcoholic fatty [NAFLD]) scope
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population. NAFLD is more common in people who are overweight, hypertensive or have type 2 diabetes mellitus.

d) The rate of progression of NAFLD is variable. Older age (around 45–50 years), being overweight and having diabetes are all associated with an increased risk of progressive disease.

e) NAFLD will progress to cirrhosis in some people. A proportion of these will die from liver failure or hepatocellular cancer or need a liver transplant.

f) In addition to excessive morbidity and mortality from liver disease, NAFLD is associated with an increased cardiovascular morbidity and mortality and excess mortality from cancer.

3.2 Current practice

a) NAFLD is usually diagnosed in primary care incidentally either by abnormal liver blood tests or an abnormal liver ultrasound appearance picked up as part of an investigation for an unrelated condition.

b) The care pathway in primary care for someone with suspected NAFLD is unclear, and practice regarding further investigation and referral varies widely.

c) NAFLD is increasingly being identified through case finding in hospital outpatient departments for people with associated conditions such as diabetes, obesity or hypertension. However, this practice is not universal and there is no guidance about which patients should be screened for NAFLD.

d) Once people with NAFLD have been referred to secondary care, their condition may be investigated further with a liver biopsy, but because there is no guidance about which patients to biopsy, investigation tends to be ad hoc.

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e) Because there is currently no licensed treatment for NAFLD, most people are discharged back to their GP. Some are given advice on lifestyle, which is usually focused on achieving weight loss, but others are given little or no lifestyle advice.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults, children and young people with suspected or confirmed primary NAFLD.

b) No subgroups of people have been identified as needing specific consideration.

4.1.2 Groups that will not be covered

a) People with secondary causes of fatty liver (for example, chronic hepatitis C infection, total parenteral nutrition treatment and drug-induced fatty liver).

4.2 Setting

a) All primary and secondary care settings where NHS healthcare is provided or commissioned.

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4.3 Management

4.3.1 Key issues that will be covered

Assessment

a) Identification of people who may have NAFLD.

b) Diagnostic criteria for NAFLD.

c) Tools to assess severity or stage of disease (for example, liver biopsy and transient elastography).

Management

d) Non-pharmacological treatment (for example, diet and exercise).

e) Pharmacological treatment (for example, insulin sensitisers). Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication ('off-label use') may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

f) The association between NAFLD and other extra-hepatic conditions (for example, cardiovascular disease, cancer, diabetes, insulin resistance, hypertension and dyslipidaemia).

g) Pharmacological treatment for extra-hepatic conditions (for example, diabetes, insulin resistance, hypertension and dyslipidaemia) in people with NAFLD where these need to differ from existing guidance.

h) Which people with NAFLD should be monitored and followed up and how often.

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4.3.2 Issues that will not be covered

a) Management of end-stage liver disease, hepatocellular carcinoma and liver transplant associated with NAFLD.

b) Assessment and management of cirrhosis.

4.4 Main outcomes

a) Progression of NAFLD.

b) Adverse events.

c) Health-related quality of life.

4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

4.5.1 Assessment

a) In whom should NAFLD be suspected?

b) Which diagnostic methods should be used to confirm a diagnosis of NAFLD?

c) What is the usefulness of different tools to assess the severity of NAFLD?

4.5.2 Management

a) Which non-pharmacological treatments should be used in the management of NAFLD?

b) Which pharmacological treatments should be used in the management of NAFLD?

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c) What is the level of increased risk of extra-hepatic conditions that are associated with NAFLD?

d) How does having NAFLD affect the choice of pharmacological treatment for associated co-existing conditions (for example, diabetes, hypertension, and/or dyslipidaemia)?

e) Which people with NAFLD should be monitored and how often?

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in The guidelines manual.

4.7 Status

4.7.1 Scope

This is the final scope.

4.7.2 Timing

The development of the guideline recommendations will begin in July 2014.

5 Related NICE guidance

5.1 Published guidance

5.1.1 Related NICE guidance

- Lipid modification. NICE clinical guideline 181 (2014).
- Physical activity: brief advice for adults in primary care. NICE public health guidance 44 (2013).
- Walking and cycling. NICE public health guidance 41 (2012).
- Hepatitis B and C. NICE public health guidance 43 (2012).

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- SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. NICE diagnostics guidance 5 (2012).
- Hypertension. NICE clinical guideline 127 (2011).
- Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. NICE clinical guideline 115 (2011).
- Alcohol-use disorders: preventing harmful drinking. NICE public health guidance 24 (2010).
- Alcohol-use disorders: diagnosis and clinical management of alcohol-related physical complications. NICE clinical guideline 100 (2010).
- Promoting physical activity for children and young people. NICE public health guidance 17 (2009).
- Type 2 diabetes. NICE clinical guideline 87 (2009).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Obesity (update). NICE clinical guideline. Publication expected November 2014.
- Suspected cancer (update). NICE clinical guideline. Publication expected May 2015.
- Type 2 diabetes (update). NICE clinical guideline. Publication expected August 2015.
- Diabetes in children and young people. NICE clinical guideline. Publication expected August 2015.
- Assessment and management of cirrhosis. NICE clinical guideline. Publication expected May 2016.
- Hepatitis C. NICE clinical guideline. Publication date to be confirmed.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

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- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS: 5th edition
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

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Appendix B: Declarations of interest

The May 2007 version (as updated October 2008) of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

Christopher Byrne

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	None.	n/a	n/a
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a
Twelfth GDG	n/a	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
meeting (15 October 2015 - cancelled)			
Thirteenth GDG meeting (5 February 2016)			

1 **Chris Day (GDG Chair)**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	Data monitoring committees for GSK and Genfit.	Non-specific personal pecuniary interest	Declare and participate
	Non-executive director, Newcastle Upon Tyne Hospitals NHS Foundation Trust.	Non-specific personal pecuniary interest	Declare and participate
	Board member, HB Innovations.	Non-specific personal pecuniary interest	Declare and participate
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG	No change to existing	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
meeting (19 June 2015)	declarations.		
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth GDG meeting (5 February 2016)			

1 **David Fitzmaurice**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	None.	n/a	n/a
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1	No change to existing declarations.	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
April 2015)			
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth GDG meeting (5 February 2016)			

1 **Ashley Guthrie (Co-opted expert adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
Initial declaration (26 August 2014)	I have received fees for giving lectures or chairing sessions at educational meetings sponsored by Bayer and Serano Symposia in 2012.	Non-specific personal pecuniary interest	Declare and participate
	One of my brothers works for Boehringer Ingelheim.	Non-specific personal family interest	Declare and participate
Sixth GDG meeting (23 February 2015)	I have agreed to give a lecture and receive an honorarium from Bayer Healthcare in March 2015-02-15	Personal pecuniary interest	Declare and participate
Seventh GDG meeting (1 April 2015)	Lecturer at a liver study day sponsored by Bayer for which I received an honorarium.	Personal pecuniary interest	Declare and participate

2 **Jill Johnson (Co-opted expert adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
Initial declaration (1	None.	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
September 2014)			
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a

1 **Irene McGill**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	None.	n/a	n/a
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth GDG meeting (5 February 2016)			

1 **Kevin Moore (until June 2015 due to health reasons)**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	I act as an advisor for Servier, France on the Liver Specialist Committee. This committee meets three times per year and evaluates possible cases of hepatotoxicity for reporting to the EMA.	Non-specific personal pecuniary interest	Declare and participate
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a
Eight GDG	No change to existing	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
meeting (15 May 2015)	declarations.		
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a

1 **Benjamin Mullish (Specialist Trainee Adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	None.	n/a	n/a
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth GDG meeting (5 February 2016)			

1 **Philip Newsome**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	I received payment for a talk on the use of GLP-1 analogues in non-alcoholic fatty liver disease at an educational meeting in July 2013. The talk related to the class of drugs rather than a specific agent. The funding was from Novo Nordisk who manufacture Liraglutide. My talk focussed on the class of drugs and in particular a case history of a patient receiving Exenatide (manufactured by Eli Lilly).	Not current – expired July 2014	Declare and participate
	I am the Chief Investigator of a randomised controlled trial of Liraglutide in patients with non-alcoholic fatty liver disease. The study is funded by the Wellcome Trust, NIHR and also Novo Nordisk. Novo Nordisk supplied drug and placebo for the trial and also provided financial support for the clinical research fellow for 1 out of 4 years of his time in my department.	Specific non-personal pecuniary interest	Declare and withdraw from the discussions on pharmacological treatment for the extra-hepatic condition type 2 diabetes.
	I have spoken on NAFLD at a nurses meeting (June 2014) supported by Norgine for which I received an honorarium.	Non-specific personal pecuniary interest	Declare and participate
	I am the Chief Investigator of a diagnostic study sponsored by Echosens in patients with non-alcoholic fatty liver disease. The study is funded by Echosens and compares CAP (assessment of fat) with liver	Specific non-personal pecuniary interest	Declare and withdraw from the discussions on assessment tools for i) the diagnosis and ii) the progression of NAFLD.

GDG meeting	Declaration of interest	Classification	Action taken
	biopsy. Echosens provide some costs to the recruiting centres to cover blood sampling, which has been processed by the R&D department. The study is portfolio adopted.		
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	Provided consultancy advice on trial design in NAFLD as part of advisory board for Intercept UK.	Non-specific personal pecuniary interest	Declare and participate
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	Lumena (Shire) – advisory board. Discussion of apical sodium dependent bile transporter inhibitors in NASH. The drug is not licensed, nor do Lumena/Shire manufacture any products of relevance to NAFLD.	Non-specific personal pecuniary interest	Declare and participate
	Boehringer Ingelheim – advisory board. Discussion of VAP1 inhibitors in the treatment of NAFLD. VAP1 inhibitors are not licensed but BI do manufacture products that are of relevance to the guideline (mgt of hypertension/dyslipidaemia). Payment was made to the	Specific non-personal pecuniary interest	Declare and withdraw from the discussions on pharmacological treatment for the extra-hepatic conditions hypertension and dyslipidaemia.

GDG meeting	Declaration of interest	Classification	Action taken
	University of Birmingham, School of Immunity and Infection.		
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth GDG meeting (5 February 2016)			

1 **Tanja Pardela**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	None.	n/a	n/a
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1	No change to existing declarations.	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
April 2015)			
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth GDG meeting (5 February 2016)			

1 **Rachel Pryke**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	I have recently been paid to give 3 talks on obesity by Janssen Cilag as part of a new diabetic drug promotion.	Non-specific personal pecuniary interest	Declare and participate
	I am a current member of the Lancet Liver Disease commission and has been unpaid.	Specific personal non-pecuniary interest	Declare and participate
	My work programme at RCGP and the RCGP Nutrition committee has received funding to cover costs from Nutricia, in view of their interest in the malnutrition agenda. I have not received any direct payments from Nutricia.	Non-specific non-personal pecuniary interest	Declare and participate
	I obtained funding from Public Health England for RCGP to develop 6 e-learning sessions on obesity and malnutrition. This funding all went directly to RCGP.	Non-specific non-personal pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	Speaker fee for attending RCGP Conference 2nd October 2014 in order to man a stand on bariatric surgery in conjunction with RCGP Nutrition Group and BOMSS, funded by Ethicon. The stand focuses on bariatric surgery care and post surgical follow up.	Non-specific personal pecuniary interest	Declare and participate
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	I have been appointed as a NICE Fellow for 3 years running from 1 April 2015 to 31 March 2018.	Non-specific personal non-pecuniary interest	Declare and participate
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	Co-author of Lancet Commission report Implementation of Lancet standing commission on liver disease in the UK due to publish in November 2015.	Specific personal non-pecuniary interest	Declare and participate
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth			

GDG meeting	Declaration of interest	Classification	Action taken
GDG meeting (5 February 2016)			

1 **Jane Putsey**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	I have none, but my father had shares in GlaxoSmithKline which he has now sold.	n/a	n/a
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a
Twelfth GDG	n/a	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
meeting (15 October 2015 - cancelled)			
Thirteenth GDG meeting (5 February 2016)			

1 **Roy Sherwood (Co-opted expert adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	None.	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a

2 **Dina Tiniakos (Co-opted expert adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
Initial declaration (10 June 2014)	None.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a

3 **Michael Trenell (Co-opted expert adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
Initial declaration (10 May 2014)	None.	n/a	n/a
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October	No change to existing declarations.	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
2014)			
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a

1 **Indra van Mourik**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	None.	n/a	n/a
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh GDG meeting (1 April 2015)	No change to existing declarations.	n/a	n/a
Eight GDG meeting (15 May 2015)	No change to existing declarations.	n/a	n/a
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth GDG meeting (5 February 2016)			

1 **Bronwen Williams**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (11 July 2014)	Currently project managing a piece of research on NAFLD in the community using an IT-based integrated care pathway.	Specific non-personal pecuniary interest	Declare and participate
	I am in the process of applying for grant funding for an Integrated Care Pathway NAFLD project based in primary care. The funding application opportunity is with the Health Foundation – 'Innovating for Improvement'. The application is at the 'first call' stage only. Deadline for submission 5 August 2014.	Specific non-personal pecuniary interest	Declare and participate
Second GDG meeting (4 September 2014)	No change to existing declarations.	n/a	n/a
Third GDG meeting (3 October 2014)	No change to existing declarations.	n/a	n/a
Fourth GDG meeting (20 November 2014)	No change to existing declarations.	n/a	n/a
Fifth GDG meeting (9 January 2015 - cancelled)	n/a	n/a	n/a
Sixth GDG meeting (23 February 2015)	No change to existing declarations.	n/a	n/a
Seventh	No change to existing	n/a	n/a

GDG meeting	Declaration of interest	Classification	Action taken
GDG meeting (1 April 2015)	declarations.		
Eight GDG meeting (15 May 2015)	On 1st May 2015, the Hepatology Research Team at the Hull Royal Infirmary received funding from Health Foundation: Innovating for Improvement programme for a primary / secondary care ICP project looking at diagnosis, referral and e-consult clinics for NAFLD. There will be an element of operational research to be conducted alongside the project which is currently being developed, but will focus on effectiveness of the NAFLD ICP model to support GPs in primary care and NAFLD patient outcomes. I will be the project manager/advisor for this project.	Non-specific non-personal pecuniary interest	Declare and participate
Ninth GDG meeting (19 June 2015)	No change to existing declarations.	n/a	n/a
Tenth GDG meeting (17 July 2015)	No change to existing declarations.	n/a	n/a
Eleventh GDG meeting (3 September 2015)	No change to existing declarations.	n/a	n/a
Twelfth GDG meeting (15 October 2015 - cancelled)	n/a	n/a	n/a
Thirteenth GDG meeting (5 February 2016)			

1 **NCGC team**

GDG meeting	Declaration of interest	Classification	Action taken

GDG meeting	Declaration of interest	Classification	Action taken
Initial declaration	In receipt of NICE commissions.	n/a	n/a

NETSCC team

GDG meeting	Declaration of interest	Classification	Action taken
Initial declaration	None.	n/a	n/a

1 Appendix C: Clinical review protocols

2 C.1 Risk factors for NAFLD

3 **Table 1: Review protocol: Risk factors for NAFLD**

Review question	Which risk factors for NAFLD or severe NAFLD (NASH, fibrosis) aid in the identification of people who should be investigated further?
Objectives	To determine the risk of NAFLD or severe NAFLD for people with different risk factors (to provide guidance on who should be investigated for diagnosis rather than relying on opportunistic case finding).
Population	• Adults (18 years and over) • Young people (11 years or older and younger than 18 years) and children (younger than 11 years)
Prognostic variable	• Waist circumference • BMI • Raised triglycerides • Low HDL-cholesterol • Type 2 diabetes (HOMA-IR, HbA1c) • Hypertension (Blood pressure; systolic or diastolic) • Age • Combinations of the above
Outcomes	• Diagnosis of NAFLD • Diagnosis of NASH/fibrosis
Review strategy	Prospective and retrospective cohorts with multivariate analysis that adjust for ≥3 of the above confounders in their model.
Exclusions	• Studies that state fewer than 3 of the above risk factors in the adult population (unless no other multivariate studies available for the young people population) • Studies with fewer than 10 participants per confounder for both the adult and young people population • Stepwise multivariate analysis (unless no other multivariate analysis studies available). • Univariate-based analysis • Conference abstracts.
How the information will be searched	The databases to be searched are Medline, Embase, the Cochrane Library. Studies will be restricted to English language only
Key confounders	Factors independently associated with prognostic variable: • Waist circumference • BMI • Raised triglycerides • Low HDL-cholesterol • Type 2 diabetes • Hypertension • Age • Vitamin D levels

C.2 Diagnosis of NAFLD

Table 2: Review protocol: Diagnosis of NAFLD

Review question	What is (are) the appropriate investigation(s) for diagnosing NAFLD in adults, young people and children?
Objectives	To evaluate the accuracy of the diagnostic tests for NAFLD. To compare the accuracy of the diagnostic tests.
Study design	Prospective and retrospective diagnostic accuracy cohort studies
Population	Combined population of adults (18 years and over), children and young people (aged >5 years to <18 years)
Index test(s)	• Alanine transaminase (ALT) • Aspartate aminotransferase (AST) • Controlled Attenuation Parameter (CAP) test (M probe, XL probe) • Fatty liver index (FLI) (0–100 scale:<30 not fatty liver, >60 is fatty liver) • Gamma GT • MRI or MRS (MRS-looking at fat in a small area in the liver) • NAFLD liver fat score • Steatotest • Liver ultrasound • Combination of tests
Reference standard	Liver biopsy (for example, NAFLD activity score [NAS] [synonymous with NASH-CRN])
Statistical measures	Diagnostic accuracy: • Sensitivity • Specificity • Positive predictive value • Negative predictive value • Positive likelihood ratio • Negative likelihood ratio • ROC curve or area under curve (AUC)
Exclusions	Post-liver transplant studies
Search strategy	The databases to be searched are Medline, Embase, the Cochrane Library. Studies will be restricted to English language only Conference abstracts will be excluded
Review strategy	Any combination(s) of tests identified. Diagnostic meta-analysis will be undertaken if appropriate (when there are 3 or more studies where 2x2 data are available for the same threshold (or agreed similar). Pooling within specific threshold ranges in consultation with GDG. In recognition that NAFLD is a partly clinical diagnosis (assessment of alcohol intake) the target conditions reported by papers which will be taken into consideration for fatty liver are: steatosis 5% and 30-34% (as reported by studies). Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-2 checklist.

C.3 Diagnosing the severity of NAFLD

Table 3: Review protocol: Diagnosing the severity of NAFLD

Review question	Which assessment tools are most accurate in identifying the severity or stage of NAFLD in adults, young people and children with NAFLD?
Objective	To determine the diagnostic accuracy of tests used to diagnose the severity and different stages of NAFLD from simple steatosis to NASH, through to fibrosis and up to the point of cirrhosis (and therefore to determine which tools should be used and on whom they should be used)
Population	Combined population of adults (18 years and over), children and young people (aged >5 years to <18 years) with NAFLD (any form of diagnosis).
Index tests (assessment tools)	**For NASH** • Cytokeratin-18 • AST/ALT ratio • ALT • Ferritin • NASH test **For fibrosis (any ≥F1 or advanced ≥F3)** • Acoustic radiation force impulse imaging (ARFI) • ALT levels • AST/ALT ratio • AST-to-platelet ratio index (APRI) • BARD score • Diffusion weighted magnetic imaging • ELF test • Ferritin • Fib-4 • Fibrometer • Fibrotest • MRI • MRS • MR elastography • NAFLD fibrosis score • Shear wave elastography Transient elastography
Reference standard	Liver biopsy (graded and staged according to Brunt or Kleiner: NAFLD activity score [NAS] [synonymous with NASH-CRN])
Outcomes	Diagnostic accuracy: Specificity Sensitivity Positive predictive value Negative predictive value Positive likelihood ratio Negative likelihood ratio ROC curve or area under curve (AUC)
Exclusion	Post-liver transplant studies Secondary fatty liver

Review question	Which assessment tools are most accurate in identifying the severity or stage of NAFLD in adults, young people and children with NAFLD?
	Conference abstracts
Search strategy	The databases to be searched are Medline, Embase, the Cochrane Library. Studies will be restricted to English language only
The review strategy	Prospective diagnostic cohorts; if none identified, retrospective diagnostic cohorts. Any combination(s) of tests identified. Diagnostic meta-analysis will be undertaken if appropriate (when there are 3 or more studies where 2x2 data are available for the same threshold (or agreed similar). Pooling within specific threshold ranges in consultation with GDG. In recognition that NAFLD is a partly clinical diagnosis (assessment of alcohol intake) the target conditions reported by papers which will be taken into consideration for fatty liver are: steatosis 5% and 30-34% (as reported by studies). Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-2 checklist. Severity of disease: • simple steatosis to non-alcoholic steatohepatitis (NASH) • fibrosis focusing on any fibrosis (F≥1) and advanced fibrosis (≥F3) • cross refer to cirrhosis guideline for specific occurrence of fibrosis F4.

C.4 Monitoring NAFLD progression

Table 4: Review protocol: Monitoring NAFLD progression

Review question	How often should we monitor adults, young people and children with NAFLD or NASH (with or without fibrosis) to determine risk of disease progression?
Objectives	To identify the rate of progression in people with NAFLD and hence who (for example, people with severe NAFLD) should be monitored for disease progression and how often.
Population	• Adults with NAFLD (18 years and over) • Young people with NAFLD (11 years or older and younger than 18 years), children with NAFLD (younger than 11 years)
Presence / absence of prognostic variable	Presence of NAFLD
Outcomes	Rate of: • Progression from NAFLD to NASH • Progression from NASH to NASH with fibrosis • Progression from NASH with fibrosis to cirrhosis
Exclusions	• Univariate-based analysis • Conference abstracts • Multivariate analysis that adjust for <3 of the above confounders • Cross-sectional design
How the information will be searched	The databases to be searched are Medline, Embase, and The Cochrane Library. Studies will be restricted to English language only
Key confounders	To be identified; factors independently associated with prognostic variable:

Review question	How often should we monitor adults, young people and children with NAFLD or NASH (with or without fibrosis) to determine risk of disease progression?
	• Waist circumference • BMI • Raised triglycerides • Low HDL-cholesterol • Type 2 diabetes • Hypertension • Age
The review strategy	RCTs, systematic reviews and Prospective and retrospective cohorts, (where multivariate analysis that state ≥3 of the above risk factors). Where studies have adjusted for more than the 3 critical confounders the results will be presented with a description.

C.5 Extra-hepatic conditions

Table 5: Review protocol: Extra-hepatic conditions

Review question	Should a diagnosis of NAFLD in adults, young people and children prompt assessment for additional extra-hepatic conditions and, if so, which?
Objectives	To determine the level of increased risk of extra-hepatic conditions associated with NAFLD.
Population	Adults (18 years and over), young people (11 years or older to younger than 18 years) and children (younger than 11 years and older than 5 years) with NAFLD.
Prognostic variable	Presence of NAFLD
Outcomes	Critical: • Cardiovascular disease (MI, stroke, TIA, angina, PAD, hypertension) • Type 2 diabetes • Colorectal cancer • Dyslipidaemia (hypertriglyceridemia) Important: • Polycystic ovarian syndrome (PCOS) for adults and young people • Chronic kidney disease (CKD) • Obstructive sleep apnoea syndrome • Vitamin D levels • Obesity (BMI) • Insulin resistance
Review strategy	Prospective and retrospective cohorts, and case–control studies with multivariate analysis that adjust for ≥3 of the above confounders in their model. While the presence of NAFLD was the primary prognostic variable identified by the GDG, papers will also be included which investigate the relationship between severity/stage of NAFLD and the identified extra-hepatic conditions.
Other exclusions	Conference abstracts, cross-sectional studies, univariate analysis, multivariate analysis that adjust for <3 listed confounders.
Search strategy	The databases to be searched are Medline, Embase, the Cochrane Library.

	Studies will be restricted to English language only
Key confounders	Critical confounders: • BMI • Gender • Age • Diabetes (needs to be adjusted for only because it's a risk factor for CVD) Important confounders: • Metabolic syndrome • Blood pressure

C.6 Weight reduction interventions

Table 6: Review protocol: Weight reduction interventions

Review question	**What is the clinical and cost-effectiveness of dietary interventions for weight reduction for adults, young people and children with NAFLD compared with standard care?**
Guideline condition and its definition	Non-alcoholic fatty liver disease (NAFLD)
Objectives	To estimate the effectiveness and cost-effectiveness of dietary interventions that are intended to result in weight reduction in the management of people with NAFLD.
Review population	People with NAFLD
	Adults > 18 years Young people; 11 to 18 years and children; younger than 11 years
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Weight reduction; Low fat Weight reduction; Low carbohydrate Weight reduction; High protein Weight reduction; High fibre Weight reduction; Higher percentage fat Weight reduction; Lower percentage fat Weight reduction; Higher percentage carbohydrate Weight reduction; Lower percentage carbohydrate Weight reduction; Higher percentage protein Weight reduction; Lower percentage protein Weight reduction; Very low calorie diet (VLCD)/extreme restriction/meal replacement Placebo / active control; Placebo Placebo / active control; Active control No intervention / standard care; No intervention No intervention / standard care; Standard care
Outcomes	- Quality of life at >3 months to <6 months (Continuous) CRITICAL - Length of stay at >3 months (Continuous) IMPORTANT - Hospitalisation at >3 months (Dichotomous) IMPORTANT - NAFLD progression with liver biopsy at 12 months and greater (Continuous) CRITICAL - NAFLD progression with MRI / MRS at 12 months and greater (Continuous) CRITICAL - NAFLD progression with ultrasound at 12 months and greater (Continuous) CRITICAL - NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 6 months to

	>12 months (Continuous) CRITICAL - Liver function tests (for example ALT levels, ALT/AST ratio) at >3 months to <6 months (Continuous) CRITICAL - NAFLD progression with fibroscan/ transient elastography at >3 months to <6months (Continuous) CRITICAL - NAFLD progression with NAFLD fibrosis score at >3 months to <6 months (Continuous) CRITICAL - Weight loss at >3 months and < 6 months (Continuous) IMPORTANT - NAFLD progression with fibroscan/ transient elastography at 6 months to <12 months (Continuous) CRITICAL - NAFLD progression with fibroscan/ transient elastography at 12 months and greater (Continuous) CRITICAL - NAFLD progression with NAFLD fibrosis score at 12 months and greater (Continuous) CRITICAL - NAFLD progression with NAFLD fibrosis score at 6 months to <12 months (Continuous) CRITICAL - Liver function tests (for example ALT levels, ALT/AST ratio) at 12 months and greater (Continuous) CRITICAL - Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months (Continuous) CRITICAL - NAFLD progression with liver biopsy at 6 months to <12 months (Continuous) CRITICAL - NAFLD progression with liver biopsy at >3 months to <6 months (Continuous) CRITICAL - NAFLD progression with ultrasound at 6 months to < 13 months (Continuous) CRITICAL - NAFLD progression with ultrasound at >3 months to < 6 months (Continuous) CRITICAL - NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 12 months and greater (Continuous) CRITICAL - NAFLD progression with Enhanced Liver Fibrosis (ELF) score at >3 months to <6 months (Continuous) CRITICAL - Liver function tests (for example ALT levels, ALT/AST ratio) at 12 months and greater (Continuous) CRITICAL - Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months (Continuous) CRITICAL - Quality of life at 6 months to <12 months (Continuous) CRITICAL - Quality of life at 12 months and greater (Continuous) CRITICAL - Weight loss at 12 months and greater (Continuous) IMPORTANT - Weight loss at 6 months to <12 months (Continuous) IMPORTANT - NAFLD progression with MRI / MRS at >3 months to < 6 months (Continuous) CRITICAL - NAFLD progression with MRI / MRS at 6 months to <12 months (Continuous) CRITICAL - NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater (Dichotomous) CRITICAL - NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater (Dichotomous) CRITICAL - NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater (Dichotomous) CRITICAL - Any adverse event at Greater or equal to 3 months (Dichotomous) IMPORTANT - Serious adverse event at Greater or equal to 3 months (Dichotomous) IMPORTANT - Severe adverse event at Greater or equal to 3 months (Dichotomous) IMPORTANT - Any adverse event at 3 months or greater (Dichotomous) IMPORTANT

	- Severe adverse events at 3 months or greater (Dichotomous) IMPORTANT - Serious adverse event at 3 months or greater (Dichotomous) IMPORTANT - Weight (kg) at 3 months and greater (Continuous) IMPORTANT
Study design	Systematic Review RCT Comparative prospective cohort study
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	12 weeks
Population stratification	Adults (18 years and over) Young people (11 years or older and younger than 18 years) Children (younger than 11 years) Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined)
Reasons for stratification	Combined young people and children
Subgroup analyses if there is heterogeneity	None specified
Search criteria	Databases: Date limits for search: Language:

C.7 Dietary modification and supplements

Table 7: Review protocol: Dietary modification and supplements in the management of NAFLD

Review question	What is the clinical and cost-effectiveness of dietary modifications or supplements for adults, young people and children with NAFLD compared with standard care?
Objective	To estimate the effectiveness and cost-effectiveness of dietary modifications and supplements in the management of people with NAFLD.
Population	• Adults with NAFLD (18 years and over) • Young people with NAFLD (11 years or older and younger than 18 years), and children with NAFLD (younger than 11 years) [NB adults and children pooled for Omega-3 fatty acids, but separate for probiotics and fibre/prebiotics]
Intervention	**Supplements:** • Omega-3 fatty acids • Probiotics • Fibre/prebiotic
Comparison	No intervention, standard care (for example, advice) or control

Outcomes	**Critical outcomes:**
	• Progression of NAFLD as assessed by:
	  ○ Liver biopsy
	  ○ MRI/MRS (combine as measure fat in liver)
	  ○ Ultrasound (absence of steatosis only)
	  ○ The Enhanced Liver Fibrosis (ELF) score
	  ○ Transient elastography
	  ○ NAFLD fibrosis score
	• Quality of life (for example CLDQ, EQ-5D)
	• Serious adverse events

Review question	What is the clinical and cost-effectiveness of dietary modifications or supplements for adults, young people and children with NAFLD compared with standard care?
	Important outcomes: • Weight loss • Liver function tests (ALT and AST levels) • Adverse events
Exclusion	Dietary advice/behaviour modification /counselling
	The databases to be searched are Medline, Embase, The Cochrane Library, nursing data bases, Amed (allied medicine and dietary interventions) Studies will be restricted to English language only
The review strategy	RCTs, Systematic Reviews of RCTs If no RCTs or SRs identified, prospective cohort studies Search terms: micronutrients
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Outcomes to be assessed at the following study follow-up times; • ≥3 months to <12 months • ≥12 months

C.8 Exercise interventions

Table 8: Review protocol: Exercise interventions in the management of NAFLD

Review question	What is the clinical and cost-effectiveness of exercise programmes for adults, young people and children with NAFLD compared with standard care?
Guideline condition and its definition	Non-alcoholic fatty liver disease (NAFLD)
Objectives	To estimate the clinical effectiveness and cost-effectiveness of exercise interventions in the management of people with NAFLD
Review population	People with NAFLD
	Adults > 18 years Young people; 11 to 18 years Children; younger than 11 years All ages
Line of therapy	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Exercise; Aerobic exercise / cardio-exercise Exercise; Resistance exercise / repeated muscle contraction (strength, anaerobic endurance) Exercise; High intensity training (alternate intense anaerobic and recover) Activities of daily living; physical activity (general everyday) Activities of daily living; Reducing sedentary time Control; usual care Control; sham Control; no treatment
Outcomes	**Critical outcomes:** • Progression of NAFLD as assessed by: ○ Liver biopsy (for example, NAFLD activity score [NAS] [synonymous with NASH-CRN]) ○ MRI or MRS ○ Ultrasound (absence of steatosis only)

Review question	What is the clinical and cost-effectiveness of exercise programmes for adults, young people and children with NAFLD compared with standard care?
	○ The Enhanced Liver Fibrosis (ELF) score ○ Transient elastography ○ NAFLD fibrosis score • Quality of life (for example CLDQ, EQ-5D) • Serious adverse events **Important outcomes:** • Liver function tests (for example, ALT and AST levels, ALT/AST ratio) • Weight • Adverse events Outcomes to be assessed at the following study follow-up times: • ≥3 months to <12 months • ≥12 months
Exclusion	Conference abstracts
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	12 weeks
Population stratification	Adults (18 years and over) Young people (11 years or older and younger than 18 years Children (younger than 11 years)
Reasons for stratification	Recommendations may differ for each population strata.
Sensitivity/other analysis	Ethnicity
Subgroup analyses if there is heterogeneity	None specified
Search criteria	Databases: Date limits for search: Language:

C.9 Lifestyle modification

Table 9: Review protocol: Lifestyle modification in the management of NAFLD

Review question	What is the clinical and cost-effectiveness of lifestyle modification programmes for diet and exercise interventions for adults, young people and children with NAFLD compared with diet alone, exercise alone or standard care?
Guideline condition and its definition	NAFLD
Objectives	To estimate the clinical effectiveness and cost-effectiveness of lifestyle modification interventions in the management of people with NAFLD
Review population	• Adults with NAFLD (18 years and over) • Young people with NAFLD (11 years or older and younger than 18 years), and children with NAFLD (younger than 11 years)

Interventions and comparators	Interventions: • Lifestyle modification; Any diet plus any exercise plus any behavioural therapy • Diet and exercise; Any diet with any exercise Comparators: • Control: no intervention, control, usual care • Diet: any diet • Exercise: any exercise
Outcomes	**Critical outcomes:** • Progression of NAFLD as assessed by: o Liver biopsy o MRI/MRS o Ultrasound (absence of steatosis only) o The Enhanced Liver Fibrosis (ELF) score o Transient elastography o NAFLD fibrosis score • Quality of life (for example, CLDQ, EQ-5D) • Serious adverse events **Important outcomes:** • Weight • Liver function tests (for example, ALT, AST levels, ALT/AST ratio) • Adverse events
Study design	RCT Systematic Review Prospective cohort study
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	12 weeks
Subgroup analyses if there is heterogeneity	Type of exercise • Type of exercise • Type of diet • Follow-up
Search criteria	Databases: Date limits for search: no date limit Language: English only

1C.10 Alcohol advice

2 **Table 10: Review protocol: Alcohol advice for people with NAFLD**

Review question	**Should people with NAFLD restrict their consumption of alcohol to below national recommended levels?**
Objective	To investigate the relationship between alcohol consumption and NAFLD, to identify if adults with a diagnosis of NAFLD should be advised to abstain from drinking alcohol completely or if there are safe limits.
Population	Adults with NAFLD (18 years and over)

Review question	Should people with NAFLD restrict their consumption of alcohol to below national recommended levels?
Prognostic variables	Alcohol consumption (continuous outcome) *Or* No alcohol compared with alcohol within national limits (categorical)
Key confounding factors	• Age • Diabetes • BMI
Outcomes	Critical outcomes: Progression of NAFLD as assessed by: • Liver biopsy (for example, NAFLD activity score [NAS] [synonymous with NASH-CRN]) • MRI or MRS • Ultrasound (absence of steatosis only) • The Enhanced Liver Fibrosis (ELF) score • Transient elastography • NAFLD fibrosis score
Exclusion	• Univariate analysis • Conference abstracts • Cross-sectional studies • MVA that control for <3 confounders
Search strategy	The databases to be searched are Medline, Embase, the Cochrane Library. Studies will be restricted to English language only
The review strategy	RCTs, systematic reviews and prospective and retrospective cohorts with multivariate analysis that adjust for ≥3 of the above confounders in their model.

1C.11 Fructose advice

2 **Table 11: Review protocol: Fructose advice**

Review question	Should people with NAFLD restrict their consumption of fructose or sugar (sucrose)?
Objectives	To investigate the relationship between fructose consumption and NAFLD, to identify if people with a diagnosis of NAFLD should be advised to restrict their consumption of fructose or sugar (sucrose).
Population	• Adults with NAFLD (18 years and over) • Young people with NAFLD (11 years or older and younger than 18 years) and children with NAFLD (younger than 11 years)
Presence / absence of prognostic variable	Pool these 2 types of carbohydrate, then subgroup if there is heterogeneity: • Fructose • Sugar (sucrose)
Outcomes	Critical outcomes: • Progression of NAFLD as assessed by: ○ Liver biopsy (for example, NAFLD activity score [NAS] [synonymous with NASH-CRN]) ○ MRI or MRS ○ Ultrasound (absence of steatosis only)

Review question	Should people with NAFLD restrict their consumption of fructose or sugar (sucrose)?
	○ The Enhanced Liver Fibrosis (ELF) score ○ Transient elastography ○ NAFLD fibrosis score Important outcomes: • Liver function tests (for example ALT levels, ALT/AST ratio) • Adverse events
Study design	RCTs systematic reviews cohort studies, or if none of the previous then case-control studies would be considered.
Exclusions	Univariate-based analysis Conference abstracts Cross-sectional studies Multivariate analyses that control for <3 confounders
How the information will be searched	The databases to be searched are Medline, Embase, the Cochrane Library. Studies will be restricted to English language only
Key confounders	Age BMI Diabetes

C.12 Caffeine advice

Table 12: Review protocol: Caffeine advice

Review question	Should people with NAFLD modify their consumption of caffeine from coffee?
Objectives	To determine if caffeine from coffee is a protective factor on the progression of NAFLD
Review population	Adults (18 years and over), young people (11 years or older to younger than 18 years) and children (younger than 11 years and older than 5 years) with NAFLD.
Prognostic variable	Coffee; Caffeine
Outcomes	**Critical outcomes:** • Progression of NAFLD as assessed by: ○ Liver biopsy ○ MRI/MRS ○ Ultrasound (absence of steatosis only) ○ The Enhanced Liver Fibrosis (ELF) score ○ Transient elastography ○ NAFLD fibrosis score • Serious adverse events • Quality of life **Important outcomes:** • Weight (BMI, wait circumference) • Liver function tests (for example, ALT, AST levels, ALT/AST ratio)
Study design	Systematic Review RCT

Review question	Should people with NAFLD modify their consumption of caffeine from coffee?
	Prospective or retrospective cohort studies If none of the above identified then case-control studies with multivariable analysis would be considered.
Search strategy	The databases to be searched are Medline, Embase, the Cochrane Library. Studies will be restricted to English language only

1C.13 Pharmacological interventions

2 **Table 13: Review protocol: Pharmacological interventions**

Review question	What is the clinical and cost-effectiveness of pharmacological interventions for adults, young people and children with NAFLD?
Guideline condition and its definition	NAFLD. Definition: Non-alcoholic fatty liver disease
Objectives	To estimate the clinical and cost-effectiveness of pharmacological interventions in the management of patients with NAFLD
Review population	People with NAFLD
	Greater or equal to 18 years of age <18 years of age
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Insulin sensitisers: pioglitazone Insulin sensitisers: metformin Ursodeoxycholic acid Vitamin E Pentoxifylline Statins ACE inhibitors Angiotensin II receptor blockers (ARBs) Alpha blockers Orlistat GLP-1 receptor agonists Dipeptidyl peptidase-4 DPP4 enzyme inhibitors Combination of 2 pharmacological interventions Placebo
Outcomes	- Quality of life at ≥3 to <12 months (Continuous) CRITICAL - Quality of life at ≥12 months (Continuous) CRITICAL - Mortality at ≥12 months (Time to event) CRITICAL - Mortality at ≥3 to <12 months (Time to event) CRITICAL - Progression of NAFLD at ≥3 to <12 months (Continuous) CRITICAL - Progression of NAFLD at ≥12 months (Continuous) CRITICAL - Serious adverse events at ≥3 to <12 months (Dichotomous) CRITICAL - Serious adverse events at ≥12 months (Dichotomous) CRITICAL - Adverse events at ≥12 months (Dichotomous) IMPORTANT - Adverse events at ≥3 to <12 months (Dichotomous) IMPORTANT - Liver function tests at ≥3 to <12 months (Continuous) IMPORTANT - Liver function tests at ≥12 months (Continuous) IMPORTANT
Study design	Systematic review RCT Non-randomised comparative study
Unit of randomisation	Patient
Crossover study	Not permitted

Minimum duration of study	3 months
Other exclusions	Other liver disease aetiology Conference abstracts
Population stratification	Adults Young people and children
Reasons for stratification	Differences in drug dosages and possible different responses to treatment
Sensitivity/other analysis	Pooling across doses
Subgroup analyses if there is heterogeneity	- Extra-hepatic condition (Type 2 diabetes; Insulin resistance; Hypertension; dyslipidaemia); Concomitant treatment
Search criteria	Databases: Medline, Embase, Cochrane library Date limits for search: N/A Language: Restricted to English language only

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Appendix D: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 1999, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[690] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example,

	Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost-utility analysis (most applicable). • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 1999 or later but that depend on unit costs and resource data entirely or predominantly from before 1999 will be rated as 'Not applicable'. • Studies published before 1999 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix E: Clinical article selection

Figure 1: Flow chart of clinical article selection for the review of risk factors for NAFLD

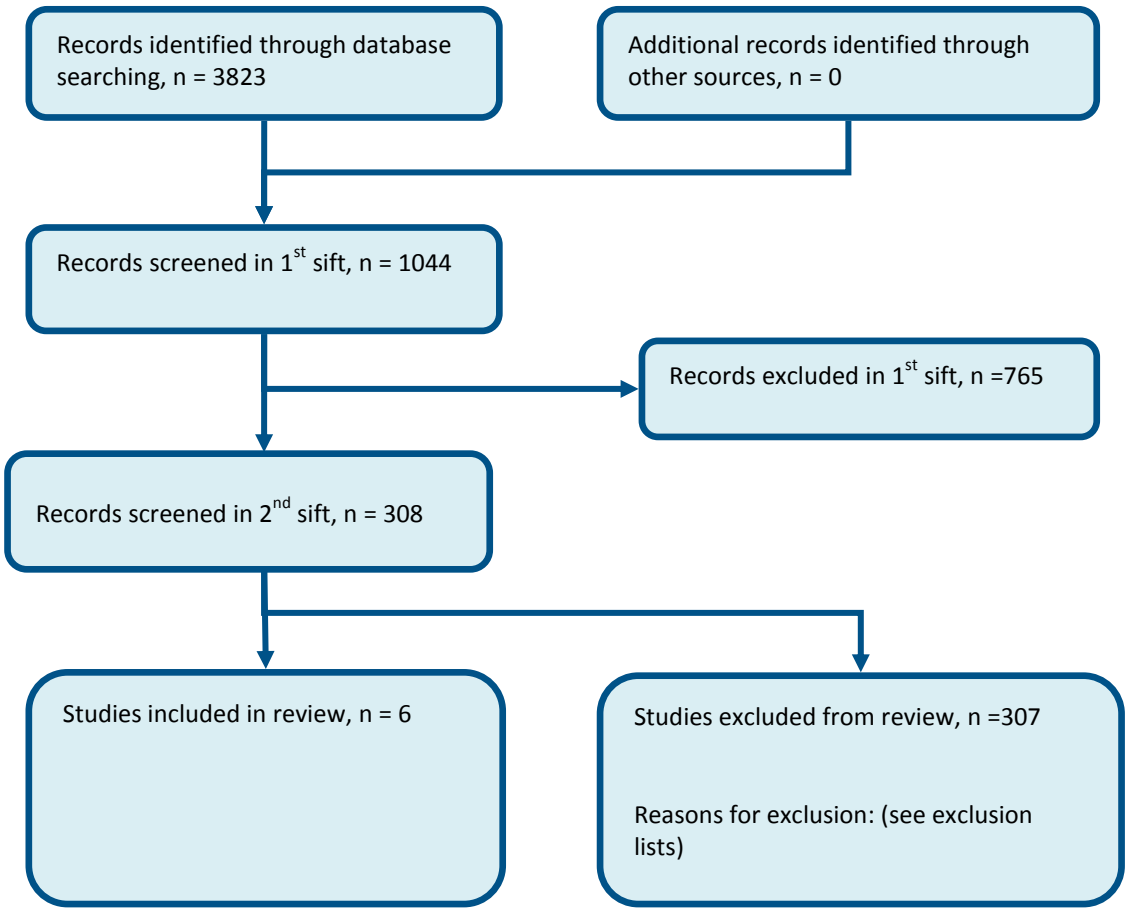
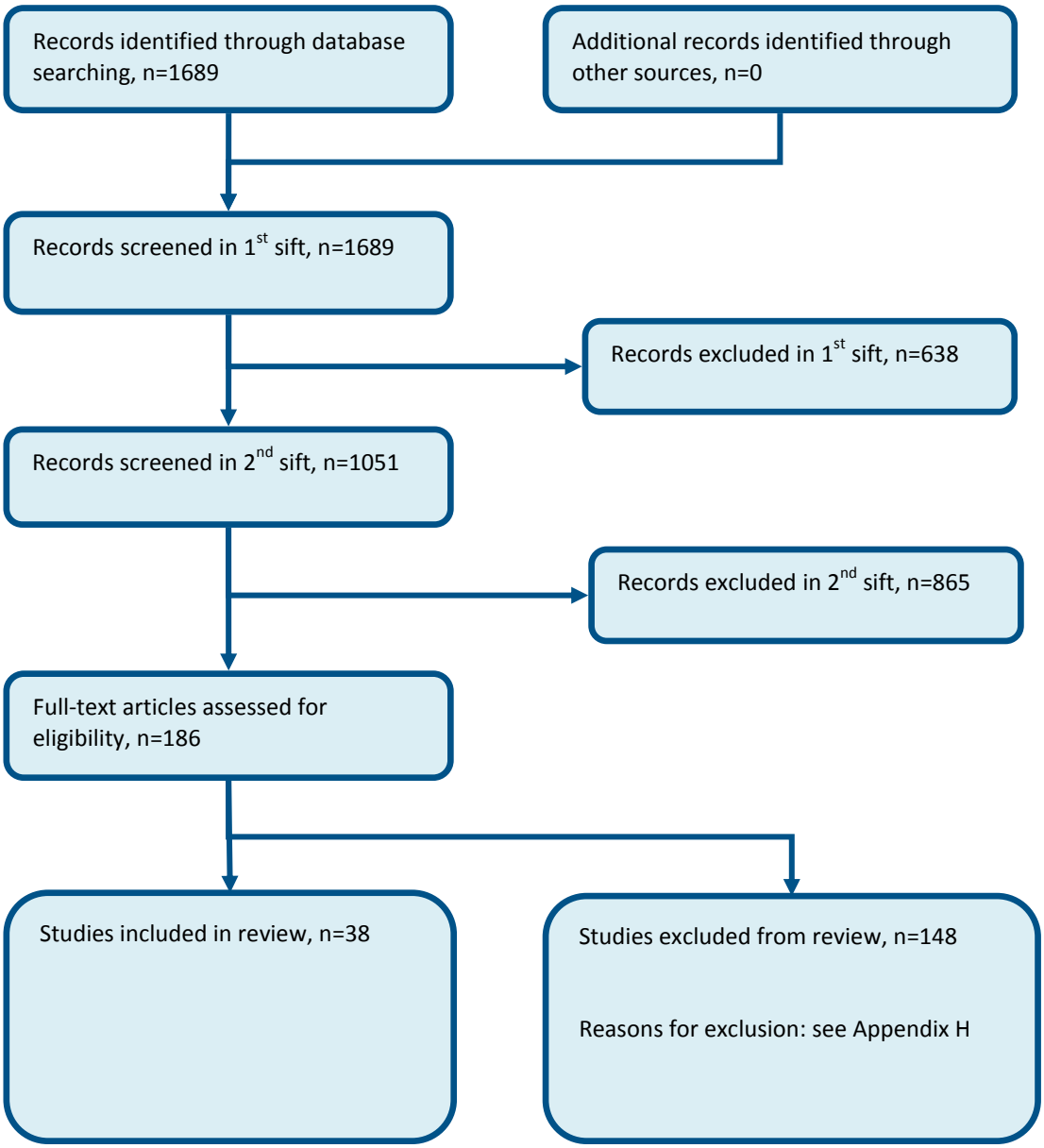
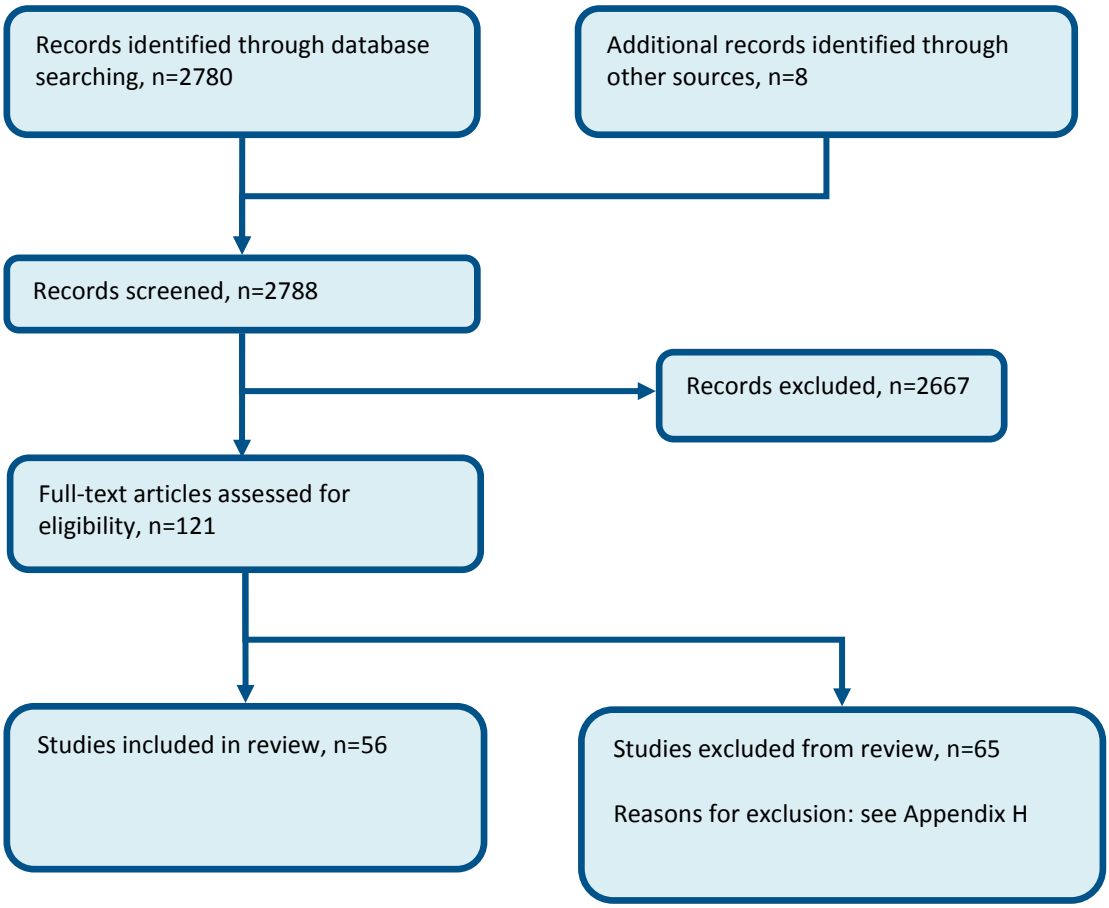


Figure 2: Flow chart of clinical article selection for the review of diagnosis of NAFLD



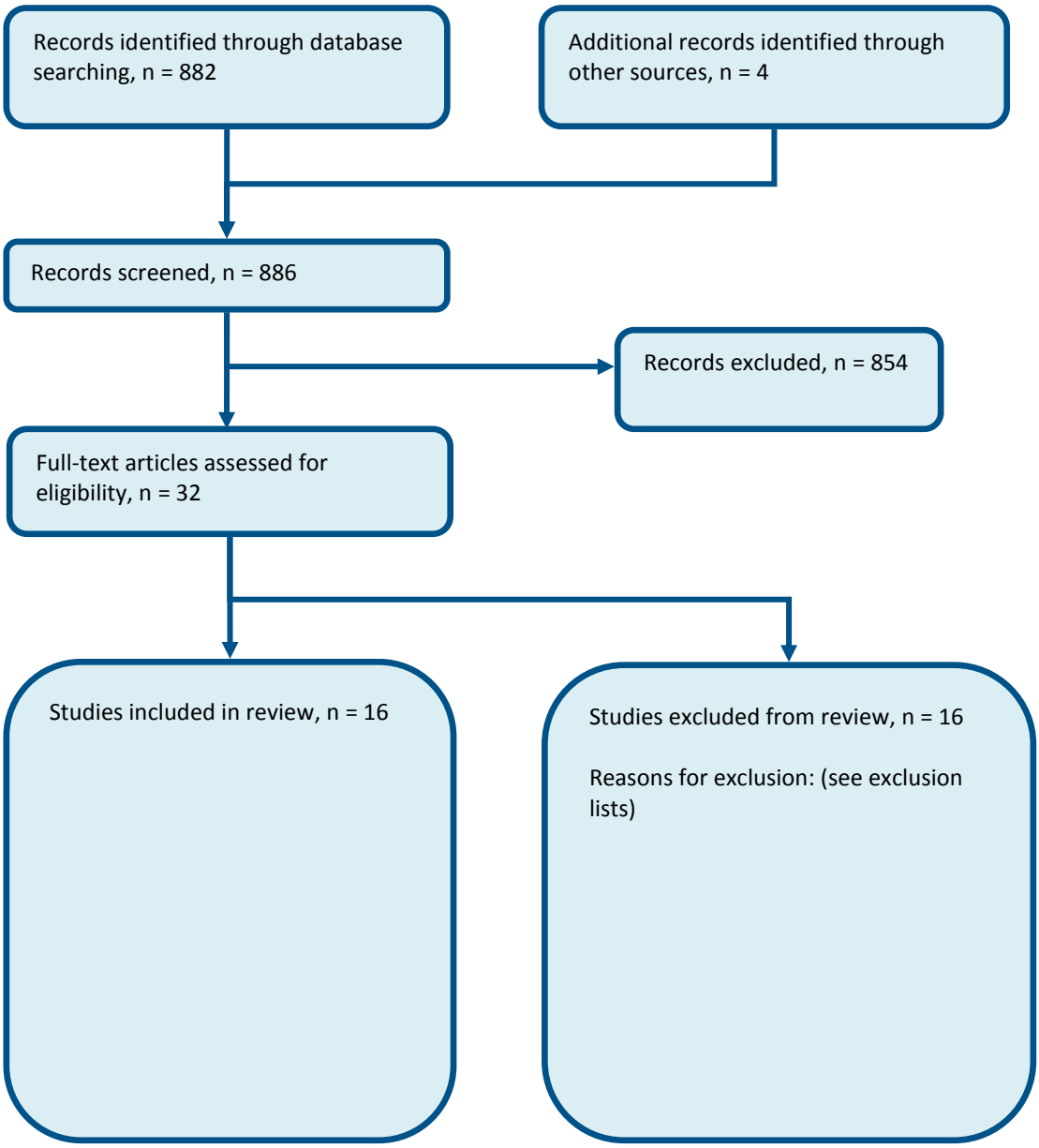
1

Figure 3: Flow chart of clinical article selection for the review of diagnosing severity of NAFLD



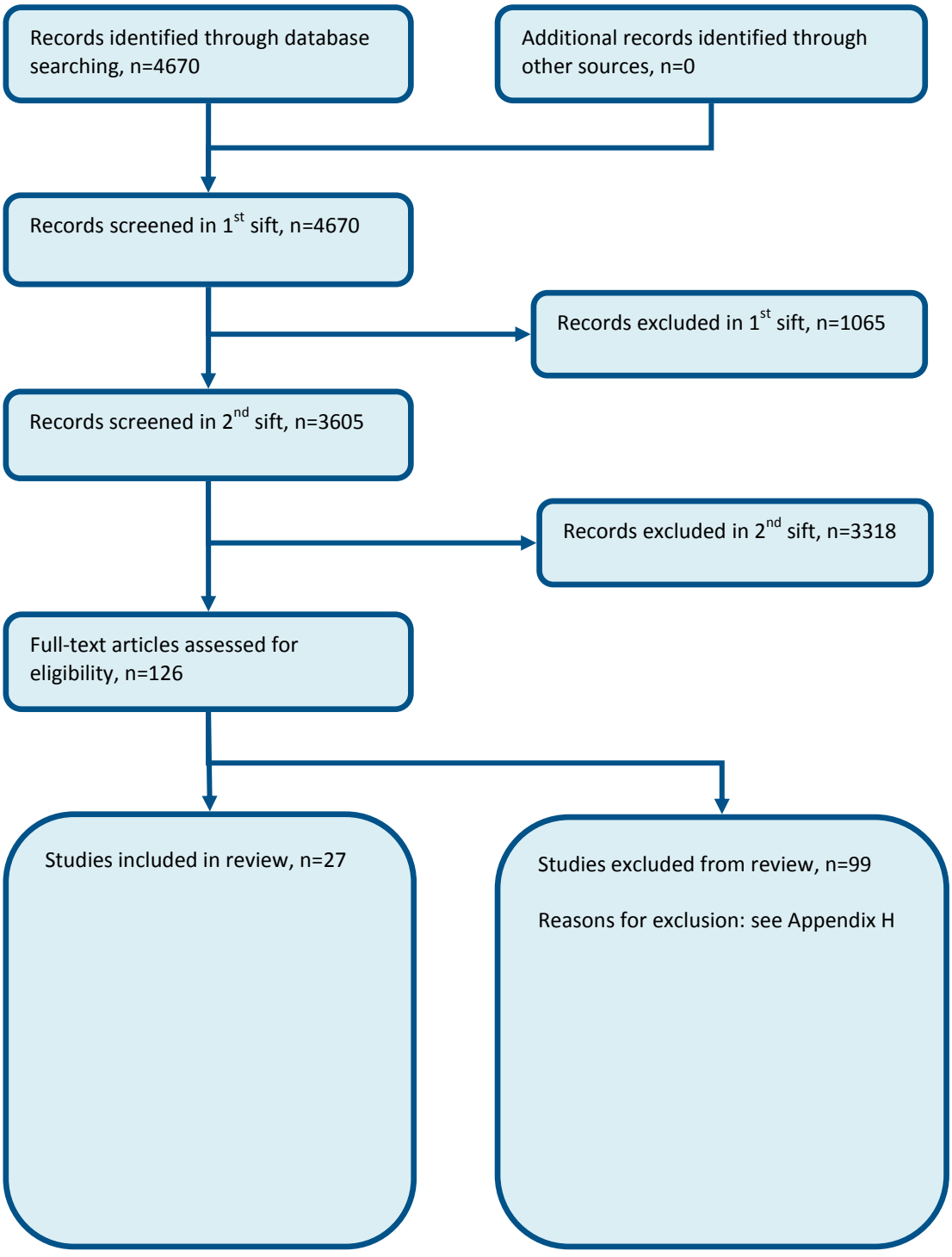
1

Figure 4: Flow diagram of article selection for the review of monitoring NAFLD progression



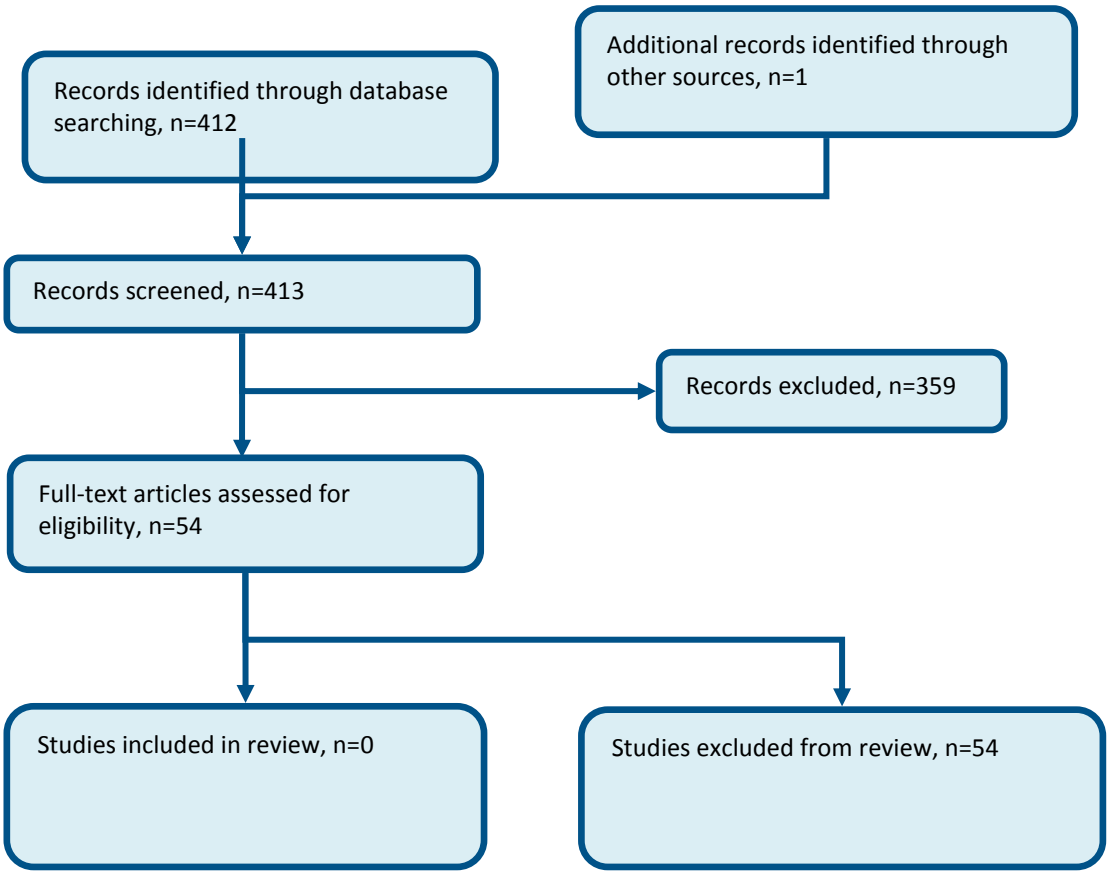
1

Figure 5: Flow chart of clinical article selection for the review of extra-hepatic conditions



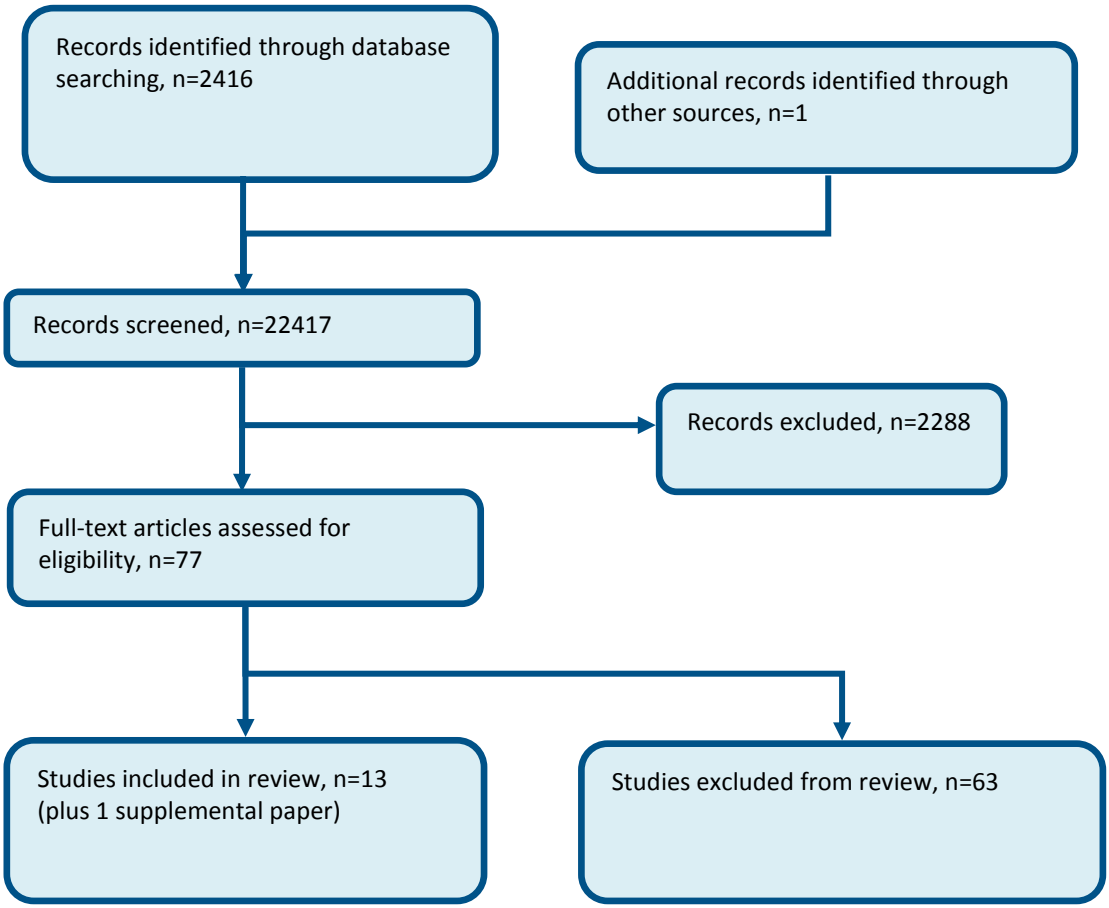
1

Figure 6: Flow chart of clinical article selection for the review of weight reduction interventions



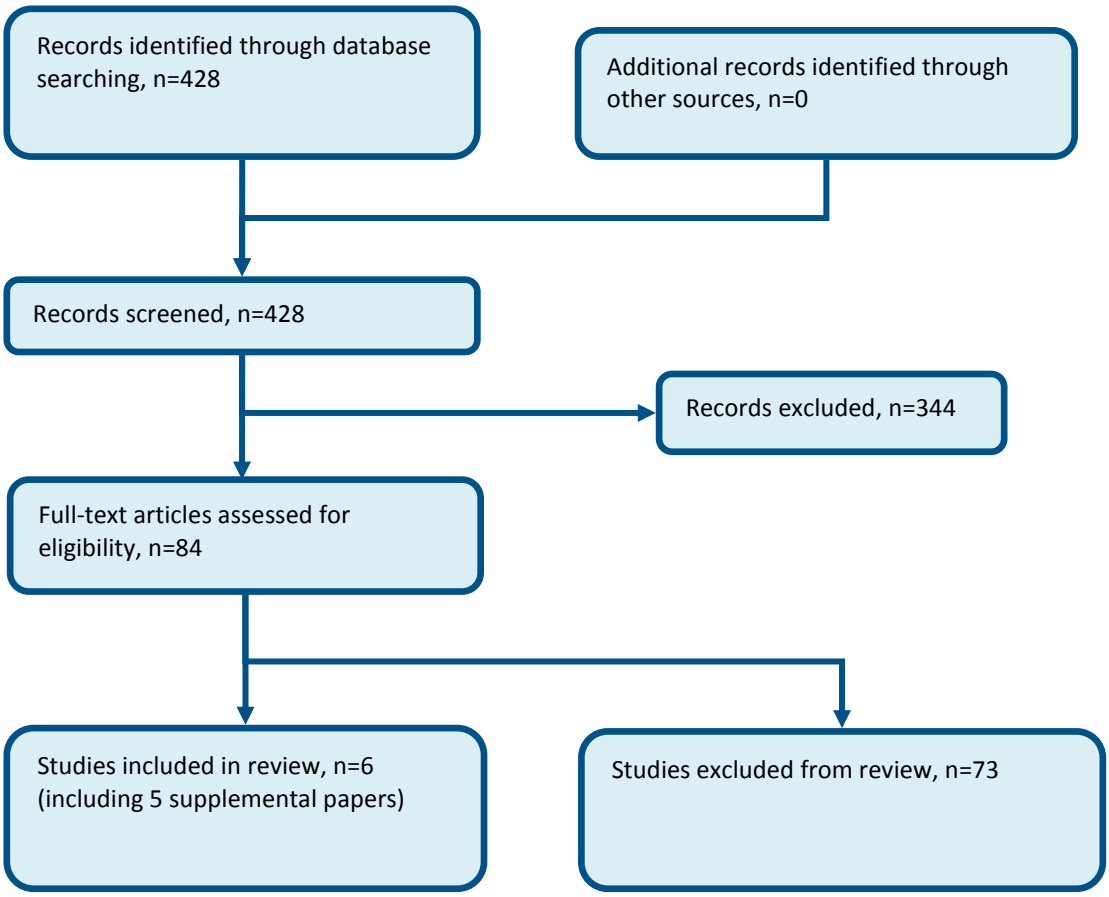
1

Figure 7: Flow chart of clinical article selection for the review of dietary supplements in the management of NAFLD



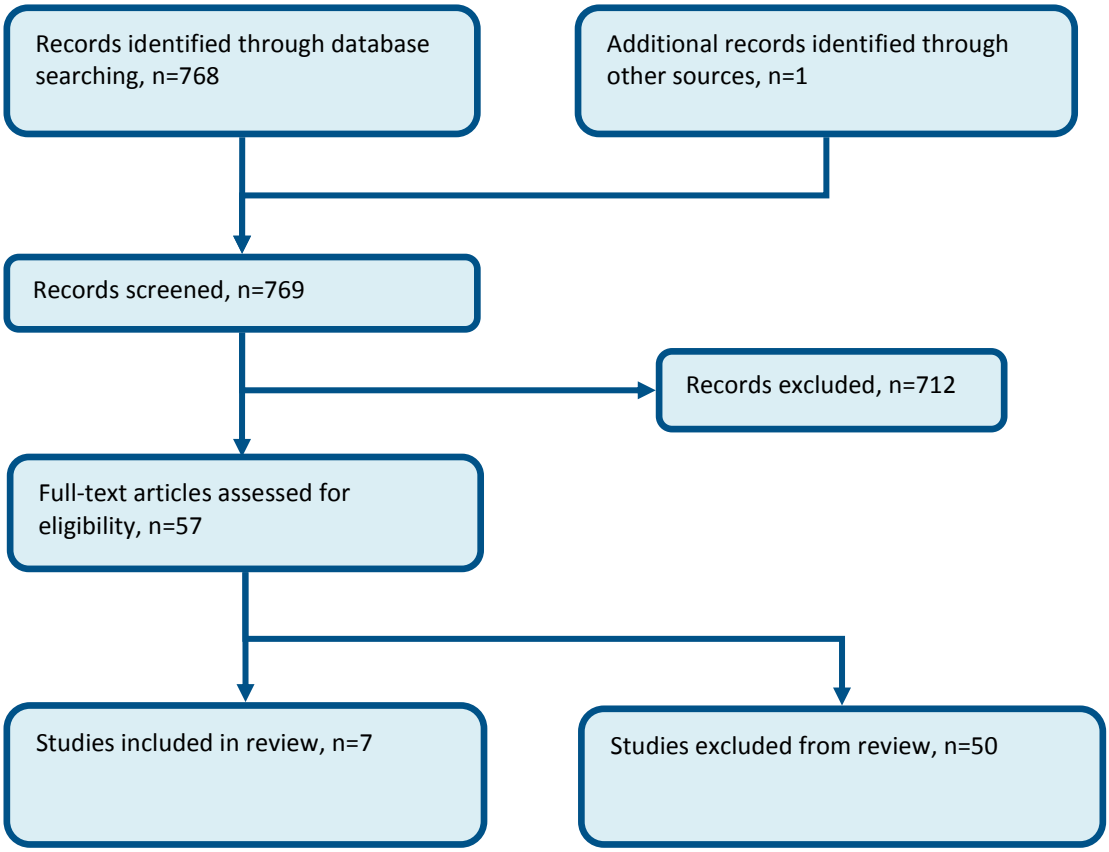
1

Figure 8: Flow chart of clinical article selection for the review of exercise in the management of NAFLD



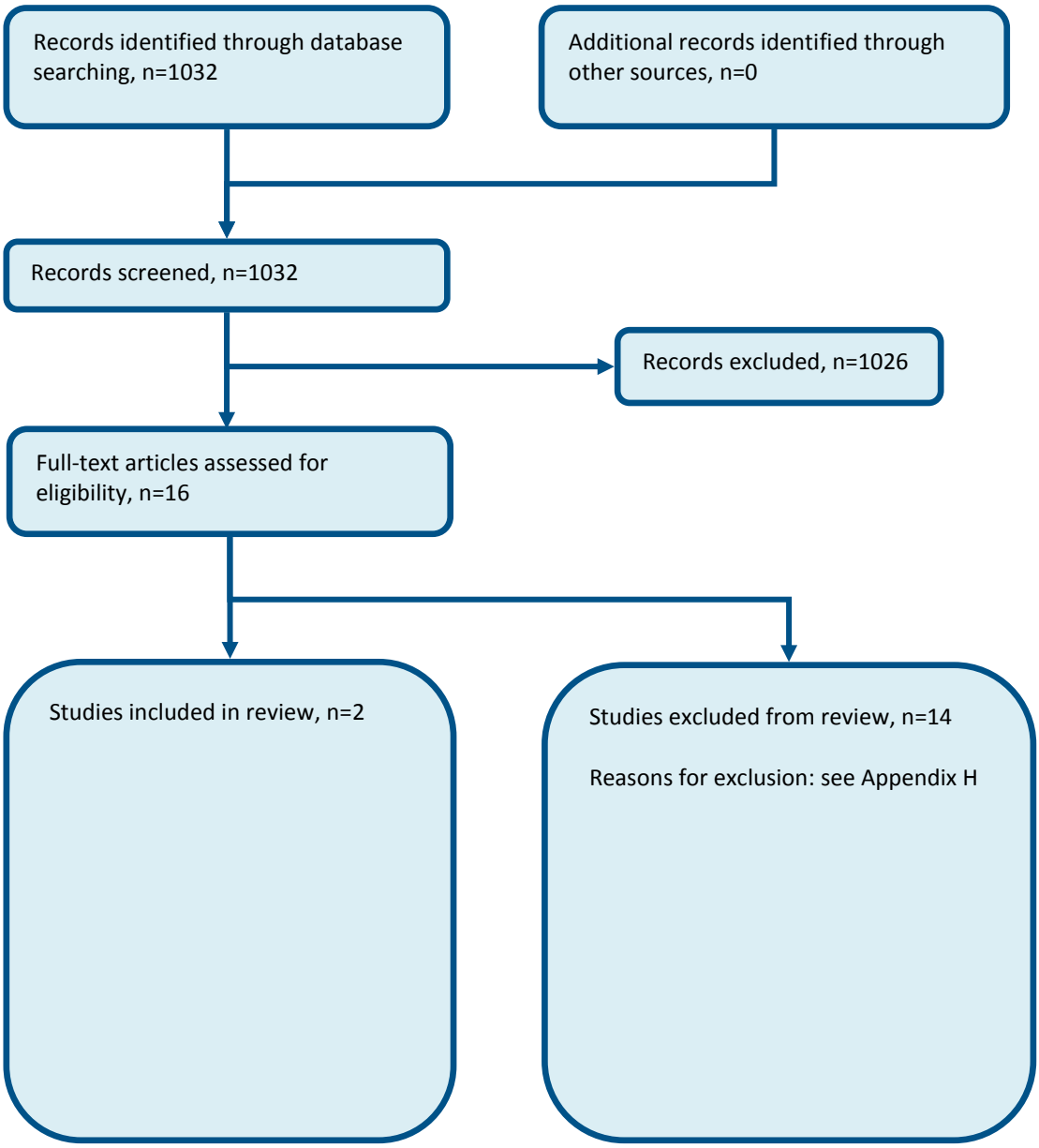
1

Figure 9: Flow chart of clinical article selection for the review of lifestyle modification for NAFLD



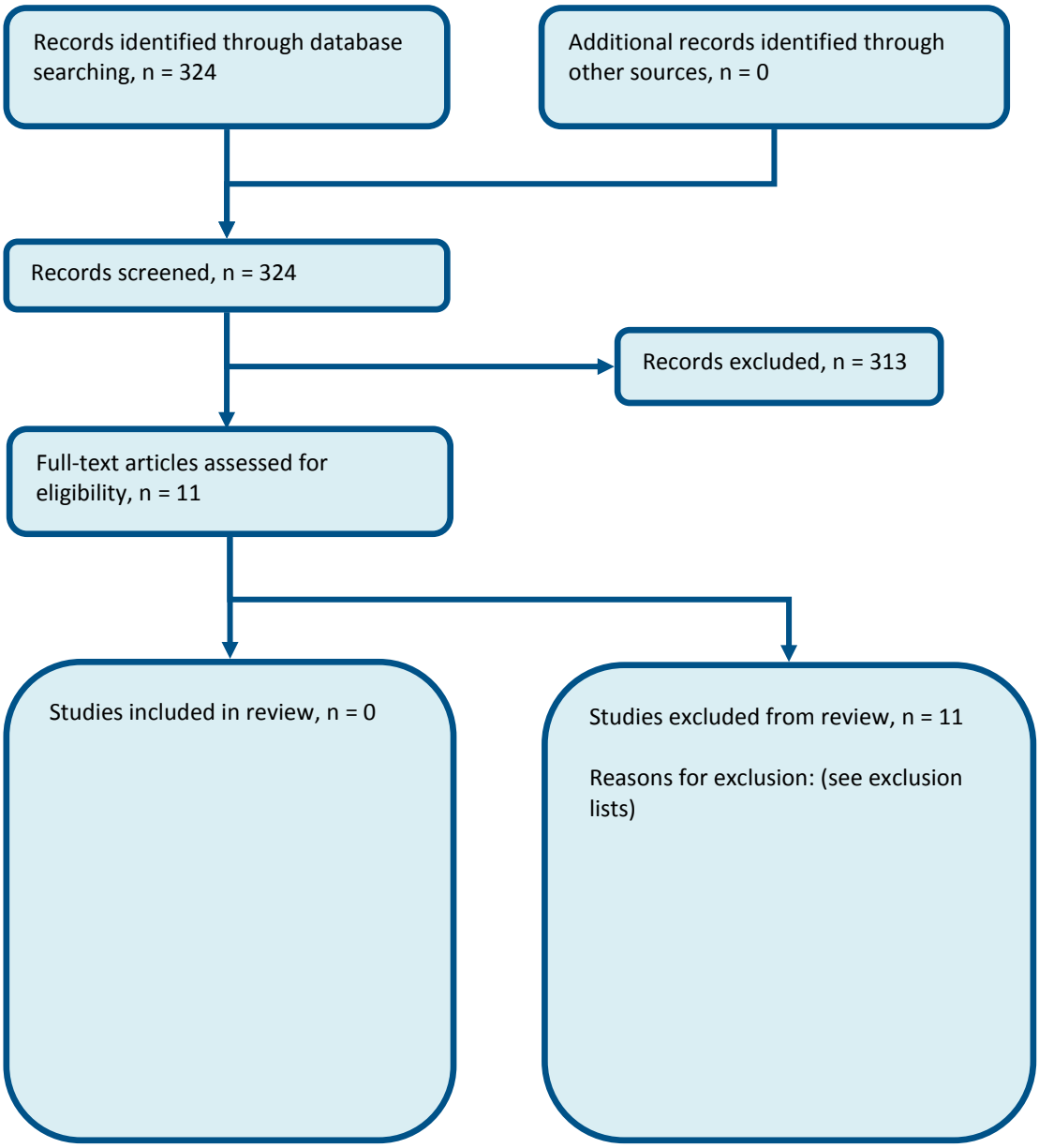
1

Figure 10: Flow chart of clinical article selection for the review of alcohol advice



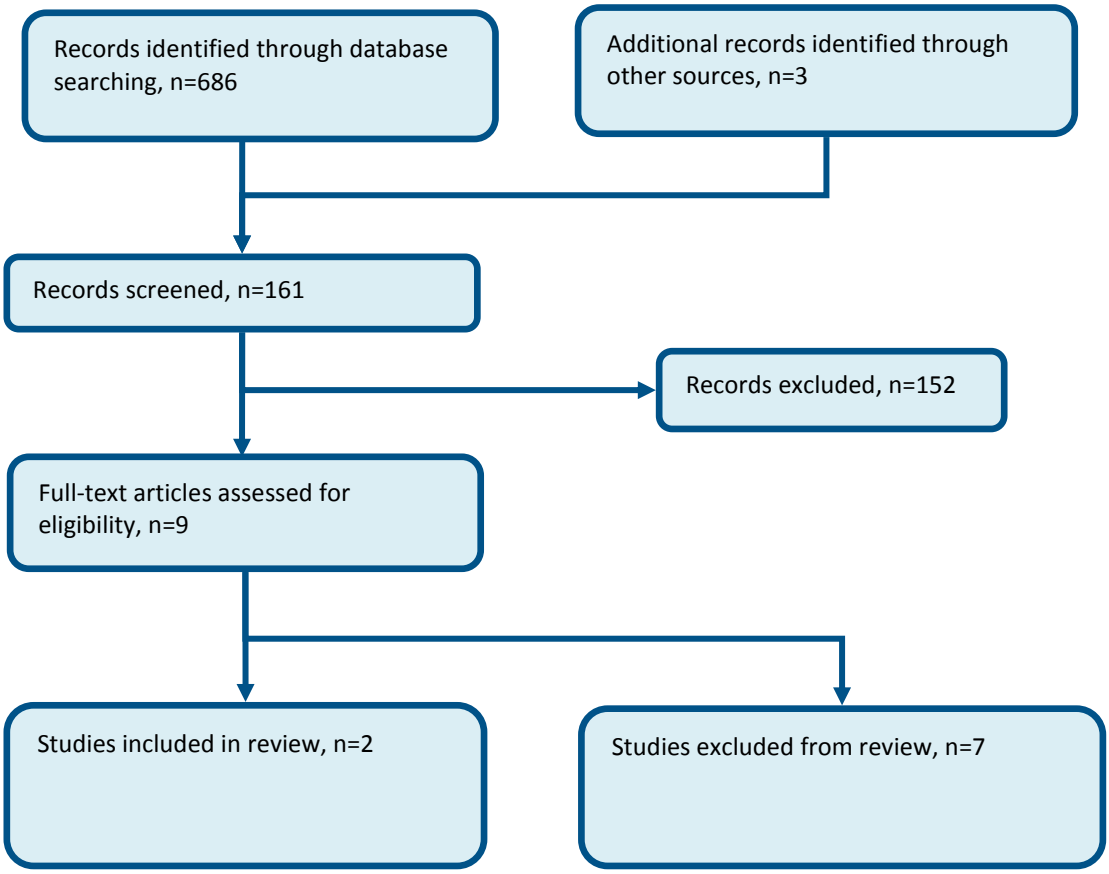
1

Figure 11: Flow diagram of article selection for review of fructose advice



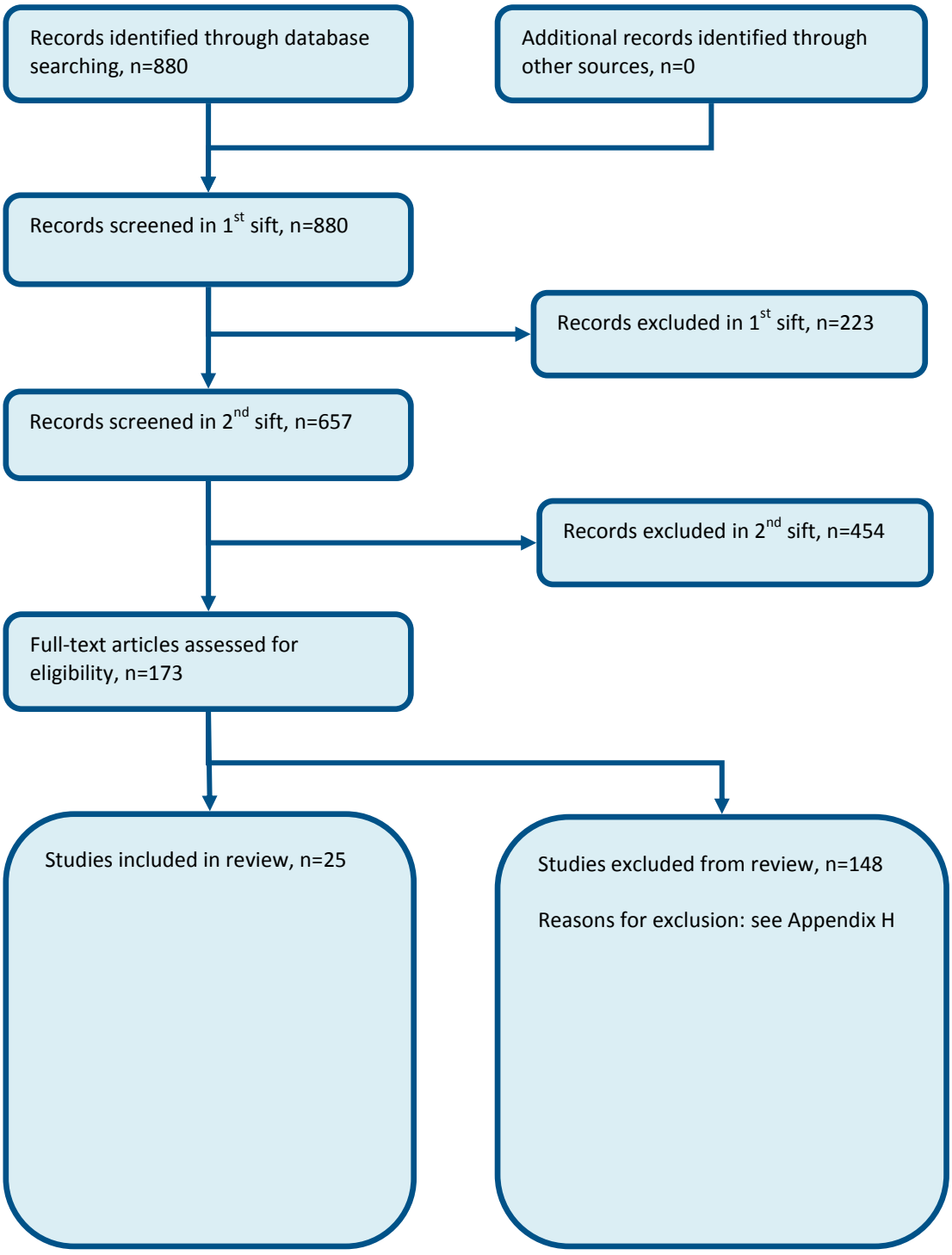
1

Figure 12: Flow chart of clinical article selection for the review of caffeine advice



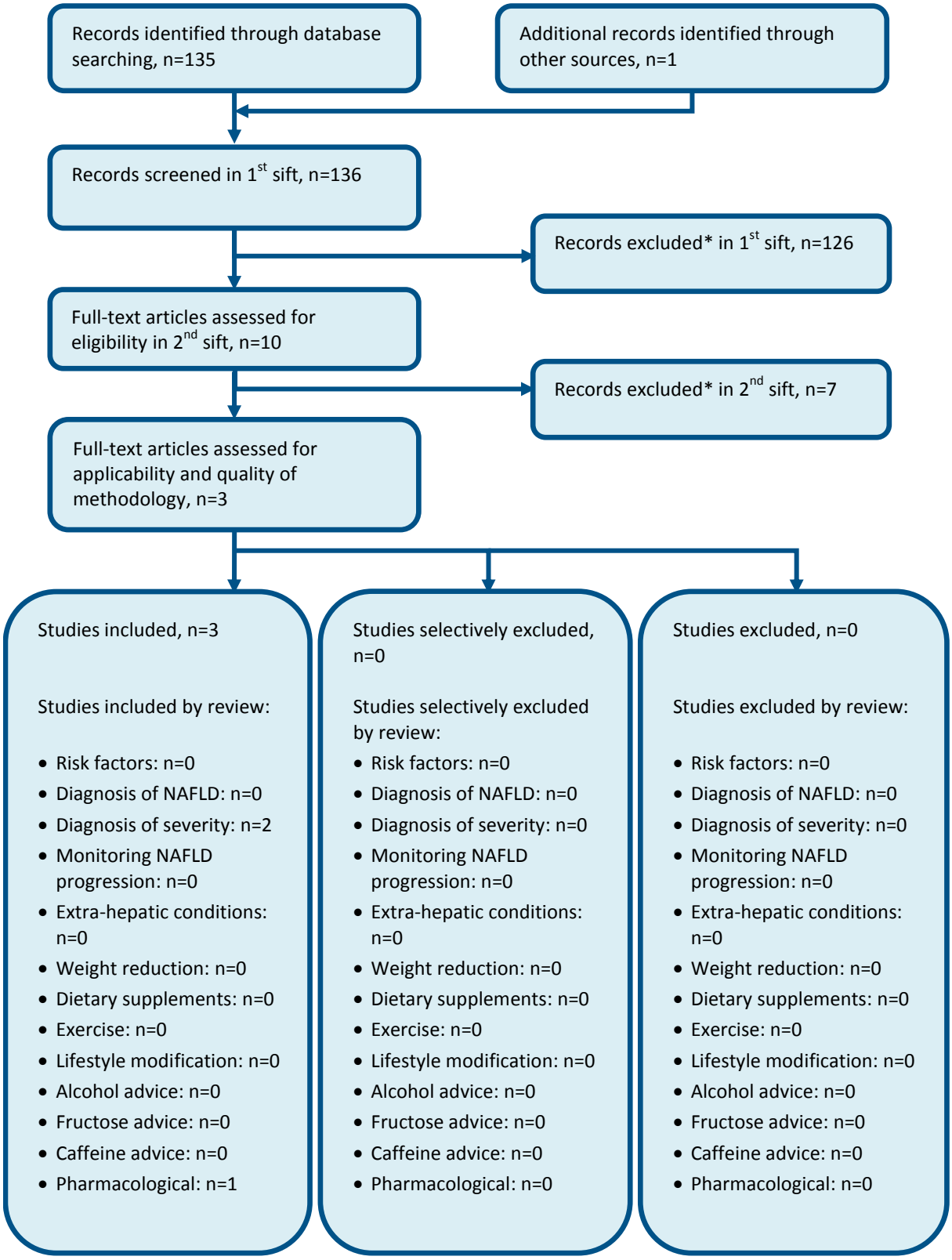
1

Figure 13: Flow chart of clinical article selection for the review of pharmacological interventions



1 # Appendix F: Health economic article selection

Figure 14: Flow chart of economic article selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Literature search strategies

Contents

Search strategies used for the non-alcoholic fatty liver disease (NAFLD) guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual 2012.[690] All searches were run up to **27 August 2015,** unless otherwise stated. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. We do not routinely search for electronic, ahead of print or 'online early' publications. Where possible searches were limited to retrieve material published in English.

Table 14: Database date parameters

Database	Dates searched
Medline	1946 – 27 August 2015
Embase	1974 – 27 August 2015
The Cochrane Library	Cochrane Reviews to 2015 Issue 8 of 12 CENTRAL to 2015 Issue 8 of 12 DARE, HTA and NHSEED to 2015 Issue 2 of 4
AMED	1985 – 27 August 2015
CINAHL	1981 – 27 August 2015
PsycINFO	1967 – 27 August 2015

Table 15: Databases searched

Question	Question number	Databases
Alcohol	A.4.10	Medline, Embase, Cochrane Library
Assessment tools	A.4.1	Medline, Embase, Cochrane Library
Caffeine	A.4.2	Medline, Embase, Cochrane Library
Diagnosis	A.4.3	Medline, Embase, Cochrane Library
Diet	A.4.12	Medline, Embase, Cochrane Library, AMED, CINAHL
Economic modelling	A.5.3	Medline, Embase, NHS EED, CRD, HEED
Exercise	A.4.4	Medline, Embase, Cochrane Library, AMED, CINAHL
Extra-hepatic conditions	A.4.6	Medline, Embase, Cochrane Library
Fructose	A.4.5	Medline, Embase, Cochrane Library
Health economics	A.5.1	Medline, Embase, NHS EED, CRD
Lifestyle modifications	A.4.7	Medline, Embase, Cochrane Library, AMED, CINAHL, PsycINFO
Monitoring	A.4.8	Medline, Embase, Cochrane Library
Pharmacological	A.4.11	Medline, Embase, Cochrane Library
Quality of life	A.5.2	Medline, Embase, NHS EED, CRD
Risk factors	A.4.9	Medline, Embase, Cochrane Library

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in CINAHL (ESBSCO), AMED (OVID) and PsycINFO (OVID & ProQUEST) for some questions (see Table 2).

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate. Searches for **prognostic studies** were usually constructed combining population terms with prognostic variable terms and sometimes outcomes. Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (OVID), Embase (OVID), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA databases were hosted by the Centre for Research and Dissemination (CRD). The Health Economic Evaluation Database (HEED)

ceased production in 2014 with access ceasing in January 2015. For the final dates of HEED searches, please see individual economic questions. For Medline and Embase, an economic filter (instead of a study type filter) was added to the same clinical search strategy. Searches in CRD and HEED were constructed using population terms only.

Population search strategies

Standard population strategy

Medline search terms

1.	fatty liver/
2.	non-alcoholic fatty liver disease/
3.	(((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
4.	(nafl* or nash).ti,ab.
5.	or/1-4

Embase search terms

1.	nonalcoholic fatty liver/
2.	(((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
3.	(nafl* or nash).ti,ab.
4.	or/1-3

Cochrane search terms

#1.	[mh ^"fatty liver"]
#2.	MeSH descriptor: [non-alcoholic fatty liver disease] this term only
#3.	(((fatty or fat or steato*) near/3 (liver* or hepat*)) or steatohepat* or (visceral near/2 steato*)):ti,ab
#4.	(nafl* or nash):ti,ab
#5.	{or #1-#4}

CINAHL search terms

S1.	(MH "fatty liver+")
S2.	(((fatty or fat or steato*) n3 (liver* or hepat*)) or steatohepat* or (visceral n2 steato*))
S3.	(nafl* or nash)
S4.	S1 or S2 or S3

AMED search terms

1.	liver disease/
2.	(((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
3.	(nafl* or nash).ti,ab.
4.	or/1-3

Study filter search terms

Systematic review (SR) search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

1 **Embase search terms**

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

2 **Randomised controlled trials (RCT) search terms**

3 **Medline search terms**

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

4 **Embase search terms**

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/

8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

Observational studies (OBS) search terms

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

Diagnostic (DIAG) search terms

Medline search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/

7.	(roc curve* or auc).ti,ab.
8.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

Embase search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(roc curve* or auc).ti,ab.
7.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/ 1-10

Risk (RISK) search terms

Medline search terms

1.	exp risk/
2.	prevalence/
3.	incidence/
4.	(risk* or prevalence* or incidence* or predict* or associat*).ti.
5.	or/ 1-4

Embase search terms

1.	exp *risk/
2.	*prevalence/
3.	*incidence/
4.	(risk* or prevalence* or incidence* or predict* or associat*).ti,ab.
5.	or/1-4

Health economics (HE) search terms

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/

10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

Quality of life (QoL) search terms

Medline search terms

1.	quality-adjusted life years/
2.	sickness impact profile/
3.	(quality adj2 (wellbeing or well-being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.

19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

1 **Embase search terms**

1.	quality adjusted life year/
2.	"quality of life index"/
3.	short form 12/ or short form 20/ or short form 36/ or short form 8/
4.	sickness impact profile/
5.	(quality adj2 (wellbeing or well-being)).ti,ab.
6.	sickness impact profile.ti,ab.
7.	disability adjusted life.ti,ab.
8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
22.	or/1-21

2 **Economic modelling (MOD) search terms**

3 **Medline search terms**

1.	exp models, economic/
2.	*models, theoretical/
3.	*models, organizational/
4.	markov chains/
5.	monte carlo method/
6.	exp decision theory/
7.	(markov* or monte carlo).ti,ab.
8.	econom* model*.ti,ab.
9.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
10.	or/ 1-9

4 **Embase search terms**

1.	statistical model/
2.	exp economic aspect/
3.	1 and 2
4.	*theoretical model/
5.	*nonbiological model/

6.	stochastic model/
7.	decision theory/
8.	decision tree/
9.	monte carlo method/
10.	(markov* or monte carlo).ti,ab.
11.	econom* model*.ti,ab.
12.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
13.	or/3-12

Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/

13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

CINAHL search terms

S1.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website

Searches for specific questions

Assessment tools

- Which assessment tool is most accurate in identifying the severity or stage of NAFLD?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	biological markers/
6.	alanine transaminase/
7.	exp aspartate aminotransferases/
8.	keratin-18/
9.	ferritin/
10.	or/5-9
11.	(test* or measure* or level* or diagnos* or ratio or score*).ti,ab.
12.	10 and 11
13.	(fibro test* or fibro-test* or fibrometer or fibroscan or fib4 or fib-4).ti,ab.
14.	((nafld or bard or ferritin* or fibrosis) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.
15.	((glutamic-pyruvic transaminase or glutamic-oxaloacetic transaminase or sgot or sgpt or alt or ast) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.
16.	(aspartate adj2 (aminotransferase or apoaminotransferase or transaminase) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.
17.	(alanine adj2 (aminotransferase or transaminase) adj4 (test* or measure* or level * or ratio or score*)).ti,ab.
18.	((ast-to-platelet ratio index or apri or elf or enhanced liver fibrosis or nash) adj4 (test* or measure* or level* or score*)).ti,ab.
19.	((biomarker* or marker*) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.
20.	exp magnetic resonance spectroscopy/
21.	exp diffusion magnetic resonance imaging/
22.	(elastogra* or sonoelastogra* or elasticity imag* or sheer wave).ti,ab.
23.	(acoustic radiation force impulse or arfi).ti,ab.

24.	((diffusion or weighted) adj2 (imag* or mri)).ti,ab.
25.	(mrs or ((nmr or magnetic or mr) adj2 spectroscop*)).ti,ab.
26.	or/12-25
27.	4 and 26
28.	Study filters OBS (0) or DIAG (0)
29.	27 and 28
	See Table 14 for date parameters

1 **Embase search terms**

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	biological marker/
6.	alanine aminotransferase/
7.	exp aspartate aminotransferases/
8.	cytokeratin 18/
9.	ferritin/
10.	or/5-9
11.	(test* or measure* or level* or diagnos* or ratio or score*).ti,ab.
12.	10 and 11
13.	(fibro test* or fibro-test* or fibrometer or fibroscan or fib4 or fib-4).ti,ab.
14.	((nafld or bard or ferritin* or fibrosis) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.
15.	((glutamic-pyruvic transaminase or glutamic-oxaloacetic transaminase or sgot or sgpt or alt or ast) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.
16.	(aspartate adj2 (aminotransferase or apoaminotransferase or transaminase) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.
17.	(alanine adj2 (aminotransferase or transaminase) adj4 (test* or measure* or level * or ratio or score*)).ti,ab.
18.	((ast-to-platelet ratio index or apri or elf or enhanced liver fibrosis or nash) adj4 (test* or measure* or level* or score*)).ti,ab.
19.	((biomarker* or marker*) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.
20.	exp nuclear magnetic resonance spectroscopy/
21.	exp diffusion weighted imaging/
22.	(elastogra* or sonoelastogra* or elasticity imag* or sheer wave).ti,ab.
23.	(acoustic radiation force impulse or arfi).ti,ab.
24.	((diffusion or weighted) adj2 (imag* or mri)).ti,ab.
25.	(mrs or ((nmr or magnetic or mr) adj2 spectroscop*)).ti,ab.
26.	or/12-25
27.	4 and 26
28.	Study filters OBS (0) or DIAG (0)
29.	27 and 28
	See Table 14 for date parameters

2 **Cochrane search terms**

#1.	Standard population (0)

#2.	MeSH descriptor: [biological markers] this term only
#3.	MeSH descriptor: [alanine transaminase] this term only
#4.	MeSH descriptor: [aspartate aminotransferases] explode all trees
#5.	MeSH descriptor: [keratin-18] this term only
#6.	MeSH descriptor: [ferritins] this term only
#7.	{or #2-#6}
#8.	(test* or measure* or level* or ratio or diagnos* or score*):ti,ab
#9.	#7 and #8
#10.	(fibro test* or fibro-test* or fibrometer or fibroscan or fib4 or fib-4):ti,ab
#11.	((nafld or bard or ferritin* or fibrosis) near/4 (test* or measure* or level* or ratio or score*)):ti,ab
#12.	((glutamic-pyruvic transaminase or glutamic-oxaloacetic transaminase or sgot or sgpt or alt or ast) near/4 (test* or measure* or level* or ratio or score*)):ti,ab
#13.	(aspartate near/2 (aminotransferase or apoaminotransferase or transaminase) near/4 (test* or measure* or level* or ratio or score*)):ti,ab
#14.	(alanine near/2 (aminotransferase or transaminase) near/4 (test* or measure* or level * or ratio or score*)):ti,ab
#15.	((ast-to-platelet ratio index or apri or elf or enhanced liver fibrosis or nash) near/4 (test* or measure* or level* or score*)):ti,ab
#16.	((biomarker* or marker*) near/4 (test* or measure* or level* or ratio or score*)):ti,ab
#17.	MeSH descriptor: [magnetic resonance spectroscopy] explode all trees
#18.	MeSH descriptor: [diffusion magnetic resonance imaging] explode all trees
#19.	(elastogra* or sonoelastogra* or elasticity imag* or sheer wave):ti,ab
#20.	(acoustic radiation force impulse or arfi):ti,ab
#21.	((diffusion or weighted) near/2 (imag* or mri)):ti,ab
#22.	(mrs or ((nmr or magnetic or mr) near/2 spectroscop*)):ti,ab
#23.	{or #9-#22}
#24.	#7 and #23
#25.	#1 and #24
	See Table 14 for date parameters

Caffeine

- Should people with NAFLD modify their consumption of caffeine from coffee?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	exp caffeine/
5.	coffee/
6.	(caffeine or coffee).ti,ab.
7.	or/ 4-6
8.	3 and 7
9.	Limit 8 to English language
	See Table 14 for date parameters

Embase search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	*caffeine/
5.	*coffee/
6.	(caffeine or coffee).ti,ab.
7.	or/ 4-6
8.	3 and 7
9.	Limit 8 to English language
	See Table 14 for date parameters

Cochrane search terms

#1.	Standard population (0)
#2.	[mh caffeine]
#3.	[mh ^coffee]
#4.	(caffeine or coffee):ti,ab
#5.	{or #2-#4}
#6.	#1 and #5
	See Table 14 for date parameters

Diagnosis

- What is (are) the appropriate investigation(s) for diagnosing NAFLD in adults, young people and children?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	alanine transaminase/
6.	aspartate aminotransferases/
7.	gamma-glutamyltransferase/
8.	(test* or measure* or level* or ratio*).ti,ab.
9.	or/5-7
10.	8 and 9
11.	((alanine transaminase* or alt or aspartate aminotransferase* or ast or gamma glutamyltransferase* or gamma gt or gammagt or ggt) adj4 (test* or measure* or level* or ratio*)).ti,ab.
12.	(fatty liver ind* or fli).ti,ab.
13.	(steatotest or steato test).ti,ab.
14.	liver fat scor*.ti,ab.
15.	ultrasonography/ or exp ultrasonography, doppler/
16.	(ultrasound* or ultrason* or sonograph* or echograph*).ti,ab.
17.	magnetic resonance imaging/
18.	magnetic resonance spectroscopy/

19.	(mri or mrs or ((magnetic or mr) adj2 (imag* or spectroscop*))).ti,ab.
20.	controlled attenuation parameter.ti,ab.
21.	elasticity imaging techniques/
22.	alanine transaminase/
23.	or/ 10-22
24.	4 and 23
25.	Study filters SR (0) or DIAG (0)
26.	24 and 25
	See Table 14 for date parameters

1 **Embase search terms**

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	*alanine aminotransferase/
6.	*aspartate aminotransferase/
7.	*gamma glutamyltransferase/
8.	or/ 5-7
9.	(test* or measure* or level* or ratio*).ti,ab.
10.	8 and 9
11.	((alanine transaminase* or alt or aspartate aminotransferase* or ast or gamma glutamyltransferase* or gamma gt or gammagt or ggt) adj4 (test* or measure* or level* or ratio*)).ti,ab.
12.	(fatty liver ind* or fli).ti,ab.
13.	(steatotest or steato test).ti,ab.
14.	liver fat scor*.ti,ab.
15.	*echography/ or *doppler echography/
16.	(ultrasound* or ultrason* or sonograph* or echograph*).ti,ab.
17.	*nuclear magnetic resonance imaging/
18.	*nuclear magnetic resonance spectroscopy/
19.	(mri or mrs or ((magnetic or mr) adj2 (imag* or spectroscop*))).ti,ab.
20.	controlled attenuation parameter.ti,ab.
21.	*elastography/
22.	or/ 10-21
23.	4 and 22
24.	Study filters SR (0) or DIAG (0)
25.	23 and 24
	See Table 14 for date parameters

2 **Cochrane search terms**

#1.	Standard population (0)
#2.	[mh ^"alanine transaminase"]
#3.	[mh ^"aspartate aminotransferases"]
#4.	[mh ^gamma-glutamyltransferase]
#5.	{or #2-#4}

#6.	(test* or measure* or level* or ratio*):ti,ab
#7.	#5 and #6
#8.	((alanine next transaminase* or alt or aspartate next aminotransferase* or ast or gamma next glutamyltransferase* or gamma next gt or gammagt or ggt) near/4 (test* or measure* or level* or ratio*)):ti,ab
#9.	(fatty next liver next ind* or fli):ti,ab
#10.	(steatotest or steato next test):ti,ab
#11.	liver next fat next scor*:ti,ab
#12.	[mh ^ultrasonography]
#13.	[mh "ultrasonography, doppler"]
#14.	(ultrasound* or ultrason* or sonograph* or echograph*):ti,ab
#15.	[mh ^"magnetic resonance imaging"]
#16.	[mh ^"magnetic resonance spectroscopy"]
#17.	(mri or mrs or ((magnetic or mr) near/2 (imag* or spectroscop*))):ti,ab
#18.	controlled attenuation parameter:ti,ab
#19.	[mh ^"elasticity imaging techniques"]
#20.	{or #7-#19}
#21.	#1 and #20
	See Table 14 for date parameters

Exercise

- What is the clinical and cost-effectiveness of exercise programmes for adults, young people and children with NAFLD compared with standard care?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp Exercise/
6.	exp Exercise Therapy/
7.	Sedentary Lifestyle/
8.	exercise*.ti,ab.
9.	((resist* or strength or weight or intens* or fitness) adj2 (train* or program* or therap*)).ti,ab.
10.	(anaerobic* or aerobic*).ti,ab.
11.	(HIIT or (interval* adj2 train*)).ti,ab.
12.	(physical* adj2 (activit* or exert* or fit or fitness or train* or therap*)).ti,ab.
13.	(sedentary or ((sit or sitting) adj3 time)).ti,ab.
14.	or/5-13
15.	Study filters SR (0) or RCT (0) or OBS (0)
16.	4 and 14
17.	15 and 16
	See Table 14 for date parameters

AMED search terms

1.	Standard population (0)

2.	Limit 1 to English language
3.	exp exercise/ or exp physical fitness/
4.	exp exercise therapy/
5.	sedentary lifestyle/
6.	exercise*.ti,ab.
7.	((resist* or strength or weight or intens* or fitness) adj2 (train* or program* or therap*)).ti,ab.
8.	(anaerobic* or aerobic*).ti,ab.
9.	(hiit or (interval* adj2 train*)).ti,ab.
10.	(physical* adj2 (activit* or exert* or fit or fitness or train* or therap*)).ti,ab.
11.	(sedentary or ((sit or sitting) adj3 time)).ti,ab.
12.	or/3-11
13.	2 and 12
	See Table 14 for date parameters

1 **CINAHL search terms**

S1.	Standard population (0)
S2.	Excluded study designs and publication types (0)
S3.	1 not 2
S4.	Limit 3 to English language
S5.	(MH "exercise+") or (MH "physical activity") or (MH "therapeutic exercise+") or (MH "life style, sedentary")
S6.	exercise*
S7.	((resist* or strength or weight or intens* or fitness) n2 (train* or program* or therap*))
S8.	anaerobic* or aerobic*
S9.	hiit or interval* n2 train*
S10.	(physical* n2 (activit* or exert* or fit or fitness or train* or therap*))
S11.	(sedentary or ((sit or sitting) n3 time))
S12.	S5 or S6 or S7 or S8 or S9 or S10 or S11
S13.	S4 and S12
	See Table 14 for date parameters

2 **Embase search terms**

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp *exercise/
6.	exp *kinesiotherapy/
7.	*sedentary lifestyle/
8.	exp *physical activity/
9.	exercise*.ti,ab.
10.	((resist* or strength or weight or intens* or fitness) adj2 (train* or program* or therap*)).ti,ab.
11.	(anaerobic* or aerobic*).ti,ab.
12.	(hiit or (interval* adj2 train*)).ti,ab.
13.	(physical* adj2 (activit* or exert* or fit or fitness or train* or therap*)).ti,ab.
14.	(sedentary or ((sit or sitting) adj3 time)).ti,ab.

15.	or/ 5-14
16.	Study filters SR (0) or RCT (0) or OBS (0)
17.	4 and 15
18.	16 and 17
	See Table 14 for date parameters

Cochrane search terms

#1.	Standard population (0)
#2.	[mh exercise]
#3.	[mh "exercise therapy"]
#4.	[mh ^"sedentary lifestyle"]
#5.	exercise*:ti,ab
#6.	((resist* or strength or weight or intens* or fitness) near/2 (train* or program* or therap*)):ti,ab
#7.	(anaerobic* or aerobic*):ti,ab
#8.	(hiit or (interval* near/2 train*)):ti,ab
#9.	(physical* near/2 (activit* or exert* or fit or fitness or train* or therap*)):ti,ab
#10.	(sedentary or ((sit or sitting) near/3 time)):ti,ab
#11.	{or #2-#10}
#12.	#1 and #11
	See Table 14 for date parameters

Fructose

- Should people with NAFLD restrict their consumption of fructose or sugar?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	fructose/
6.	(fructose or sugar* or levulos* or agave nectar or honey or molasses or fruit*).ti,ab.
7.	dietary sucrose/
8.	sucrose/
9.	(saccharose or sucrose).ti,ab.
10.	high fructose corn syrup/
11.	(((corn or maize or maple) adj1 syrup) or hfcs or isoglucose).ti,ab.
12.	or/ 5-11
13.	4 and 12
	See Table 14 for date parameters

Embase search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2

4.	Limit 3 to English language
5.	fructose/
6.	(fructose or sugar* or levulos* or agave nectar or honey or molasses or fruit*).ti,ab.
7.	sucrose/
8.	sugar intake/
9.	(saccharose or sucrose).ti,ab.
10.	corn syrup/
11.	(((corn or maize or maple) adj1 syrup) or hfcs or isoglucose).ti,ab.
12.	or/ 5-11
13.	4 and 12
	See Table 14 for date parameters

Cochrane search terms

#1.	Standard population (0)
#2.	MeSH descriptor: [fructose] this term only
#3.	(fructose or sugar* or levulos* or agave nectar or honey or molasses or fruit*):ti,ab
#4.	MeSH descriptor: [dietary sucrose] this term only
#5.	MeSH descriptor: [sucrose] this term only
#6.	(saccharose or sucrose):ti,ab
#7.	MeSH descriptor: [high fructose corn syrup] this term only
#8.	(((corn or maize or maple) next syrup) or hfcs or isoglucose):ti,ab
#9.	{or #2-#8}
#10.	#1 and #9
	See Table 14 for date parameters

Extra-hepatic conditions

- Should a diagnosis of NAFLD in adults, young people and children prompt assessment for additional extra-hepatic conditions and, if so, which?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp cardiovascular disease/
6.	((cardiovascular or aortic or heart or coronary artery or peripheral arterial) adj disease*).ti.
7.	(pad or cad or cvd or cva).ti.
8.	(myocardial infarct* or mi).ti.
9.	(hypertens* or high blood pressure*).ti.
10.	((cereb* or cardiovascular or haemorrhagic) adj stroke).ti.
11.	(tia or transient ischemic attack* or cerebral* ischemia*).ti.
12.	exp diabetes mellitus, type 2/
13.	(diabet* adj2 (type 2 or type2 or type ii or type two)).ti.
14.	(dm2 or t2d*).ti.

15.	(diabet* adj2 (noninsulin or non insulin or slow-onset or slow onset or adult-onset or adult onset)).ti.
16.	dyslipidemias/
17.	hyperlipidemias/
18.	(dyslipidemia* or dyslipidaemia*).ti.
19.	(hyperlipidemia* or hyperlipidaemia*).ti.
20.	hypercholesterolemia/
21.	(hypercholesterolemia or elevated cholesterol).ti.
22.	hypertriglyceridemia/
23.	(hypertriglyceridemia* or hypertriglyceridaemia*).ti.
24.	exp neoplasms/
25.	(cancer* or adenocarcinoma* or neoplasm* or tumor* or carcinoma* or myeloma*).ti.
26.	((primary or secondary) adj cancer).ti.
27.	((breast or uterus or uterine or ovarian or ovary or womb or prostate or endometrial) adj3 cancer).ti.
28.	((oesophageal or oesophagus or colorectal or colon or bowel or liver or gallbladder or pancreatic or kidney or stomach or gullet) adj3 cancer).ti.
29.	((non-hodgkin* or non hodgkin*) adj lymphoma*).ti.
30.	(lymphoma* or sarcoma* or heptoblastoma or neuroendocrine tumor).ti.
	(adenocarcinoma* adj1 (papillary or non-papillary or non papillary)).ti.
31.	(carcinoma* adj1 (b-cell or t-cell or b cell or t cell or squamous cell)).ti.
32.	(myeloma* or multiple myeloma* or myelomatosis).ti.
33.	vitamin d/
34.	(vitamin d or vit d).ti.
35.	chronic kidney disease/
36.	(chronic kidney disease or ckd).ti.
37.	polycystic ovary syndrome/
38.	(pcos or polycystic ovary syndrome).ti.
39.	exp sleep apnea syndromes/
40.	(sleep apnea syndrome or sleep apnoea syndrome or obstructive sleep apnoea sydrome or osas or osahs or osah).ti.
41.	obesity/
42.	(obesity or obese or bmi or body mass index).ti.
43.	metabolic syndrome x/
44.	(metabolic adj1 syndrom*).ti.
45.	((extra-hepatic or extrahepatic or extra hepatic) adj2 (disease* or condition*)).ti.
46.	(liver adj2 (related complication* or increas* risk or associate* risk)).ti,ab.
47.	or/ 5-46
48.	Study filters OBS (0) or RISK (0)
49.	4 and 47
50.	48 and 49
	See Table 14 for date parameters

Embase search terms

1.	Standard population (0)

2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp cardiovascular disease/
6.	((cardiovascular or aortic or heart or coronary artery or peripheral arterial) adj disease*).ti.
7.	(pad or cad or cvd or cva).ti.
8.	(myocardial infarct* or mi).ti.
9.	(hypertens* or high blood pressure*).ti.
10.	((cereb* or cardiovascular or haemorrhagic) adj stroke).ti.
11.	(tia or transient ischemic attack* or cerebral* ischemia*).ti.
12.	exp non insulin dependent diabetes mellitus/
13.	(diabet* adj2 (type 2 or type2 or type ii or type two)).ti.
14.	(dm2 or t2d*).ti.
15.	(diabet* adj2 (noninsulin or non insulin or slow-onset or slow onset or adult-onset or adult onset)).ti.
16.	dyslipidemia/
17.	hyperlipidemia/
18.	(dyslipidemia* or dyslipidaemia*).ti.
19.	(hyperlipidemia* or hyperlipidaemia*).ti.
20.	hypercholesterolemia/
21.	(hypercholesterolemia or elevated cholesterol).ti.
22.	hypertriglyceridemia/
23.	(hypertriglyceridemia* or hypertriglyceridaemia*).ti.
24.	exp neoplasm/
25.	(cancer* or adenocarcinoma* or neoplasm* or tumor* or carcinoma* or myeloma*).ti.
26.	((primary or secondary) adj cancer).ti.
27.	((breast or uterus or uterine or ovarian or ovary or womb or prostate or endometrial) adj3 cancer).ti.
28.	((oesophageal or oesophagus or colorectal or colon or bowel or liver or gallbladder or pancreatic or kidney or stomach or gullet) adj3 cancer).ti.
29.	((non-hodgkin* or non hodgkin*) adj lymphoma*).ti.
30.	(lymphoma* or sarcoma* or heptoblastoma or neuroendocrine tumor).ti.
31.	(adenocarcinoma* adj1 (papillary or non-papillary or non papillary)).ti.
32.	(carcinoma* adj1 (b-cell or t-cell or b cell or t cell or squamous cell)).ti.
33.	(myeloma* or multiple myeloma* or myelomatosis).ti.
34.	vitamin d/
35.	(vitamin d or vit d).ti.
36.	chronic kidney disease/
37.	(chronic kidney disease or ckd).ti.
38.	ovary polycystic disease/
39.	(pcos or polycystic ovary syndrome).ti.
40.	exp sleep disordered breathing/
41.	(sleep disordered breathing or sleep apnea syndrome or sleep apnoea syndrome or obstructive sleep apnoea sydrome or osas or osahs or osah).ti.
42.	obesity/
43.	(obesity or obese or bmi or body mass index).ti.

44.	metabolic syndrome x/
45.	(metabolic adj1 syndrom*).ti.
46.	((extra-hepatic or extrahepatic or extra hepatic) adj2 (disease* or condition*)).ti.
47.	(liver adj2 (related complication* or increas* risk or associate* risk)).ti,ab.
48.	or/ 5-47
49.	Study filters OBS (0) or RISK (0)
50.	4 and 48
51.	49 and 50
	See Table 14 for date parameters

1

2 **Cochrane search terms**

#1.	Standard population (0)
#2.	MeSH descriptor: [cardiovascular diseases] explode all trees
#3.	((cardiovascular or aortic or heart or coronary artery or peripheral arterial) next (disease*)):ti
#4.	(pad or cad or cvd or cva):ti
#5.	(myocardial infarct* or mi):ti
#6.	(hypertens* or high blood pressure*):ti
#7.	((cereb* or cardiovascular or haemorrhagic) next (stroke)):ti
#8.	(tia or transient ischemic attack* or cerebral* ischemia*):ti
#9.	MeSH descriptor: [diabetes mellitus, type 2] explode all trees
#10.	(diabet* near/2 (type 2 or type2 or type ii or type two)):ti
#11.	(dm2 or t2d*):ti
#12.	(diabet* near/2 (noninsulin or non insulin or slow-onset or slow onset or adult-onset or adult onset)):ti
#13.	MeSH descriptor: [dyslipidemias] explode all trees
#14.	MeSH descriptor: [hyperlipidemias] explode all trees
#15.	(dyslipidemia* or dyslipidaemia*):ti
#16.	(hyperlipidemia* or hyperlipidaemia*):ti
#17.	MeSH descriptor: [hypercholesterolemia] explode all trees
#18.	(hypercholesterolemia or elevated cholesterol):ti
#19.	MeSH descriptor: [hypertriglyceridemia] explode all trees
#20.	(hypertriglyceridemia* or hypertriglyceridaemia*):ti
#21.	MeSH descriptor: [neoplasms] explode all trees
#22.	(cancer* or adenocarcinoma* or neoplasm* or tumor* or carcinoma* or myeloma*):ti
#23.	((primary or secondary) next (cancer)):ti
#24.	((breast or uterus or uterine or ovarian or ovary or womb or prostate or endometrial) near/3 cancer):ti
#25.	((oesophageal or oesophagus or colorectal or colon or bowel or liver or gallbladder or pancreatic or kidney or stomach or gullet) near/3 cancer):ti
#26.	((non-hodgkin* or non hodgkin*) next (lymphoma*)):ti
#27.	(lymphoma* or sarcoma* or heptoblastoma or neuroendocrine tumor):ti
#28.	(adenocarcinoma* near/1 (papillary or non-papillary or non papillary)):ti
#29.	(carcinoma* near/1 (b-cell or t-cell or b cell or t cell or squamous cell)):ti
#30.	(myeloma* or multiple myeloma* or myelomatosis):ti
#31.	MeSH descriptor: [vitamin d] this term only

#32.	(vitamin d or vit d):ti
#33.	MeSH descriptor: [renal insufficiency, chronic] this term only
#34.	(chronic kidney disease or ckd):ti
#35.	MeSH descriptor: [polycystic ovary syndrome] this term only
#36.	(pcos or polycystic ovary syndrome):ti
#37.	MeSH descriptor: [sleep apnea syndromes] explode all trees
#38.	(sleep apnea syndrome or sleep apnoea syndrome or obstructive sleep apnoea sydrome or osas or osahs or osah):ti
#39.	MeSH descriptor: [obesity] explode all trees
#40.	(obesity or obese or bmi or body mass index):ti
#41.	MeSH descriptor: [metabolic syndrome x] this term only
#42.	(metabolic near/1 syndrom*):ti
#43.	((extra-hepatic or extrahepatic or extra hepatic) near/2 (disease* or condition*)):ti
#44.	(liver near/2 (related complication* or increas* risk or associate* risk)):ti,ab
#45.	{or #2-#44}
#46.	#1 and #45
#47.	MeSH descriptor: [risk] explode all trees
#48.	MeSH descriptor: [prevalence] this term only
#49.	MeSH descriptor: [incidence] this term only
#50.	(risk* or prevalence* or incidence* or predict* or associat*):ti,ab
#51.	{or #47-#50}
#52.	#46 and #51
	See Table 14 for date parameters

Lifestyle modifications

- What is the clinical and cost-effectiveness of lifestyle modification programmes for diet and exercise interventions for adults, young people and children with NAFLD compared with diet alone, exercise alone or standard care?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp diet/
6.	weight loss/
7.	exp diet therapy/
8.	diet*.ti,ab.
9.	(weight adj3 (loss* or lose or reduc* or percent*)).ti,ab.
10.	(hypocaloric or (low adj1 calorie*) or vlcd).ti,ab.
11.	((low* or reduc* or percent*) adj3 (fat* or carb*)).ti,ab.
12.	((high* or percent*) adj3 protein*).ti,ab.
13.	or/5-12
14.	exp exercise/
15.	exp exercise therapy/
16.	sedentary lifestyle/

17.	exercise*.ti,ab.
18.	((resist* or strength or weight or intens* or fitness) adj2 (train* or program* or therap*)).ti,ab.
19.	(anaerobic* or aerobic*).ti,ab.
20.	(hiit or (interval* adj2 train*)).ti,ab.
21.	(physical* adj2 (activit* or exert* or fit or fitness or train* or therap*)).ti,ab.
22.	(sedentary or ((sit or sitting) adj3 time)).ti,ab.
23.	or/14-22
24.	counseling/
25.	exp behavior therapy/
26.	motivation/
27.	social support/
28.	exp psychotherapy/
29.	managed care programs/
30.	self care/
31.	(cbt or (cognit* adj2 therap*) or (behav* adj1 therap*)).ti,ab.
32.	(mbt or (mentali#ation adj based adj1 therap*)).ti,ab.
33.	(feedback or biofeedback).ti,ab.
34.	((behav* or lifestyle or life-style) adj3 (modif* or program* or therap* or change* or treatment* or interven* or adjust*)).ti,ab.
35.	((multifactor* or multifacet* or multi-facet* or multi-factor* or managed) adj2 program*).ti,ab.
36.	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
37.	((support* or advice or advise) adj3 (telephone* or internet or online or web or app or apps or program* or group*)).ti,ab.
38.	(psychotherap* or psychosocial*).ti,ab.
39.	(psycholog* adj2 intervent*).ti,ab.
40.	(self adj3 (manage* or care or motivat*)).ti,ab.
41.	(henry or motivat* or educat*).ti,ab.
42.	((famil* or parent*) adj2 (therap* or program*)).ti,ab.
43.	or/24-42
44.	13 and 23
45.	43 and (13 or 23)
46.	44 or 45
47.	4 and 46
48.	Study filters SR (0) or RCT (0)
49.	47 and 48
	See Table 14 for date parameters

1 **AMED search terms**

1.	Standard population (0)
2.	Limit 1 to English language
3.	exp diet/
4.	exp diet therapy/
5.	weight loss/
6.	diet*.ti,ab.
7.	(weight adj3 (loss* or lose or reduc* or percent*)).ti,ab.

8.	(hypocaloric or (low adj1 calorie*) or vlcd).ti,ab.
9.	((low* or reduc* or percent*) adj3 (fat* or carb*)).ti,ab.
10.	((high* or percent*) adj3 protein*).ti,ab.
11.	or/3-10
12.	exp exercise/ or exp physical fitness/
13.	exp exercise therapy/
14.	sedentary lifestyle/
15.	exercise*.ti,ab.
16.	((resist* or strength or weight or intens* or fitness) adj2 (train* or program* or therap*)).ti,ab.
17.	(anaerobic* or aerobic*).ti,ab.
18.	(hiit or (interval* adj2 train*)).ti,ab.
19.	(physical* adj2 (activit* or exert* or fit or fitness or train* or therap*)).ti,ab.
20.	(sedentary or ((sit or sitting) adj3 time)).ti,ab.
21.	or/12-20
22.	counseling/
23.	exp psychotherapy/
24.	motivation/
25.	social support/
26.	self care/
27.	(cbt or (cognit* adj2 therap*) or (behav* adj1 therap*)).ti,ab.
28.	(mbt or (mentali#ation adj based adj1 therap*)).ti,ab.
29.	(feedback or biofeedback).ti,ab.
30.	((behav* or lifestyle or life-style) adj3 (modif* or program* or therap* or change* or treatment* or interven* or adjust*)).ti,ab.
31.	((multifactor* or multifacet* or multi-facet* or multi-factor* or managed) adj2 program*).ti,ab.
32.	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
33.	((support* or advice or advise) adj3 (telephone* or internet or online or web or app or apps or program* or group*)).ti,ab.
34.	(psychotherap* or psychosocial*).ti,ab.
35.	(psycholog* adj2 intervent*).ti,ab.
36.	(self adj3 (manage* or care or motivat*)).ti,ab.
37.	(henry or motivat* or educat*).ti,ab.
38.	((famil* or parent*) adj2 (therap* or program*)).ti,ab.
39.	or/22-38
40.	11 and 21
41.	39 and (11 or 21)
42.	40 or 41
43.	2 and 42
	See Table 14 for date parameters

CINAHL search terms

S1.	Standard population (0)
S2.	Excluded study designs and publication types (0)
S3.	1 not 2
S4.	Limit 3 to English language

S5.	(MH "exercise+") or (MH "physical activity") or (MH "therapeutic exercise+") or (MH "life style, sedentary")
S6.	exercise*
S7.	((resist* or strength or weight or intens* or fitness) n2 (train* or program* or therap*))
S8.	anaerobic* or aerobic*
S9.	hiit or interval* n2 train*
S10.	(physical* n2 (activit* or exert* or fit or fitness or train* or therap*))
S11.	(sedentary or ((sit or sitting) n3 time))
S12.	S5 or S6 or S7 or S8 or S9 or S10 or S11
S13.	(MH "diet+") or (MH "diet therapy+") or (MH "weight loss")
S14.	diet*
S15.	(weight n3 (loss* or lose or reduc* or percent*))
S16.	(hypocaloric or (low n1 calorie*) or vlcd)
S17.	((low* or reduc* or percent*) n3 (fat* or carb*))
S18.	((high* or percent*) n3 protein*)
S19.	S13 or S14 or S15 or S16 or S17 or S18
S20.	(MH "counseling") or (MH "psychotherapy+") or (MH "motivational interviewing") or (MH "motivation") or (MH "managed care programs") or (MH "self care")
S21.	(cbt or (cognit* n2 therap*) or (behav* n1 therap*))
S22.	(mbt or ((mentalization or mentalisation) n1 based n1 therap*))
S23.	feedback or biofeedback
S24.	((behav* or lifestyle or life-style) n3 (modif* or program* or therap* or change* or treatment* or interven* or adjust*))
S25.	((multifactor* or multifacet* or multi-facet* or multi-factor* or managed) n2 program*)
S26.	(psycholog* or council* or counsel* or psychotherap* or psychosocial)
S27.	((support* or advice or advise) n3 (telephone* or internet or online or web or app or apps or program* or group*))
S28.	psychotherap* or psychosocial*
S29.	psycholog* n2 intervent*
S30.	(self n3 (manage* or care or motivat*))
S31.	henry or motivat* or educat*
S32.	((famil* or parent*) n2 (therap* or program*))
S33.	S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32
S34.	S12 and S19
S35.	S12 or S19
S36.	S33 and S35
S37.	S34 or S36
S38.	S4 and S37
	See Table 14 for date parameters

1 **PsycINFO (OVID) search terms**

1.	liver disorders/
2.	(((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
3.	(nafl* or nash).ti,ab.
4.	or/1-3
5.	limit 4 to English language

6.	diets/ or weight control/
7.	diet*.ti,ab.
8.	(weight adj3 (loss* or lose or reduc* or percent*)).ti,ab.
9.	(hypocaloric or (low adj1 calorie*) or vlcd).ti,ab.
10.	((low* or reduc* or percent*) adj3 (fat* or carb*)).ti,ab.
11.	((high* or percent*) adj3 protein*).ti,ab.
12.	or/6-11
13.	exp physical activity/
14.	physical fitness/
15.	exercise*.ti,ab.
16.	((resist* or strength or weight or intens* or fitness) adj2 (train* or program* or therap*)).ti,ab.
17.	(anaerobic* or aerobic*).ti,ab.
18.	(hiit or (interval* adj2 train*)).ti,ab.
19.	(physical* adj2 (activit* or exert* or fit or fitness or train* or therap*)).ti,ab.
20.	(sedentary or ((sit or sitting) adj3 time)).ti,ab.
21.	or/13-20
22.	exp counseling/ or exp family therapy/ or exp support groups/
23.	exp behavior modification/ or exp psychotherapy/
24.	exp motivation/ or motivation training/
25.	social support/
26.	self care skills/
27.	(cbt or (cognit* adj2 therap*) or (behav* adj1 therap*)).ti,ab.
28.	(mbt or (mentali#ation adj based adj1 therap*)).ti,ab.
29.	(feedback or biofeedback).ti,ab.
30.	((behav* or lifestyle or life-style) adj3 (modif* or program* or therap* or change* or treatment* or interven* or adjust*)).ti,ab.
31.	((multifactor* or multifacet* or multi-facet* or multi-factor* or managed) adj2 program*).ti,ab.
32.	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
33.	((support* or advice or advise) adj3 (telephone* or internet or online or web or app or apps or program* or group*)).ti,ab.
34.	(psychotherap* or psychosocial*).ti,ab.
35.	(psycholog* adj2 intervent*).ti,ab.
36.	(self adj3 (manage* or care or motivat*)).ti,ab.
37.	(henry or motivat* or educat*).ti,ab.
38.	((famil* or parent*) adj2 (therap* or program*)).ti,ab.
39.	or/22-38
40.	12 and 21
41.	39 and (12 or 21)
42.	40 or 41
43.	5 and 42
	See Table 14 for date parameters

1 **PsycINFO (ProQuest) search terms**

1.	(su.exact("liver disorders") or ti,ab(((fatty or fat or steato*) near/3 (liver* or hepat*)) or steatohepat* or (visceral near/2 steato*)) or ti,ab(nafl* or nash)) and (((su.exact("diets") or su.exact("weight control") or ti,ab(diet*) or ti,ab(weight near/3 (loss* or lose or reduc* or

	percent*)) or ti,ab(hypocaloric or (low near/1 calorie*) or vlcd) or ti,ab((low* or reduc* or percent*) near/3 (fat* or carb*)) or ti,ab((high* or percent*) near/3 protein*)) and (su.exact.explode("physical activity") or su.exact("physical fitness") or ti,ab(exercise*) or ti,ab((resist* or strength or weight or intens* or fitness) near/2 (train* or program* or therap*)) or ti,ab(anaerobic* or aerobic*) or ti,ab(hiit or (interval* near/2 train*)) or ti,ab(physical* near/2 (activit* or exert* or fit or fitness or train* or therap*)) or ti,ab(sedentary or ((sit or sitting) near/3 time)))) or (((su.exact("diets") or su.exact("weight control") or ti,ab(diet*) or ti,ab(weight near/3 (loss* or lose or reduc* or percent*)) or ti,ab(hypocaloric or (low near/1 calorie*) or vlcd) or ti,ab((low* or reduc* or percent*) near/3 (fat* or carb*)) or ti,ab((high* or percent*) near/3 protein*)) or (su.exact.explode("physical activity") or su.exact("physical fitness") or ti,ab(exercise*) or ti,ab((resist* or strength or weight or intens* or fitness) near/2 (train* or program* or therap*)) or ti,ab(anaerobic* or aerobic*) or ti,ab(hiit or (interval* near/2 train*)) or ti,ab(physical* near/2 (activit* or exert* or fit or fitness or train* or therap*)) or ti,ab(sedentary or ((sit or sitting) near/3 time)))) and (su.exact.explode("counseling") or su.exact.explode("family therapy") or su.exact.explode("support groups") or su.exact.explode("behavior modification") or su.exact.explode("psychotherapy") or su.exact.explode("motivation") or su.exact("motivation training") or su.exact("social support") or su.exact("self care skills") or ti,ab(cbt or (cognit* near/2 therap*) or (behav* near/1 therap*)) or ti,ab(mbt or (mentali?ation-based near/4 therap*)) or ti,ab(feedback or biofeedback) or ti,ab((behav* or lifestyle or life-style) near/3 (modif* or program* or therap* or change* or treatment* or interven* or adjust*)) or ti,ab((multifactor* or multifacet* or multi-facet* or multi-factor* or managed) near/2 program*) or ti,ab(psycholog* or council* or counsel* or psychotherap* or psychosocial) or ti,ab((support* or advice or advise) near/3 (telephone* or internet or online or web or app or apps or program* or group*)) or ti,ab(psychotherap* or psychosocial*) or ti,ab(psycholog* near/2 intervent*) or ti,ab(self near/3 (manage* or care or motivat*)) or ti,ab(henry or motivat* or educat*) or ti,ab((famil* or parent*) near/2 (therap* or program*)))))
	Date Parameters: 2014 – 27 August 2015

1 **Embase search terms**

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp *diet/
6.	exp *diet therapy/
7.	*weight reduction/
8.	diet*.ti,ab.
9.	(weight adj3 (loss* or lose or reduc* or percent*)).ti,ab.
10.	(hypocaloric or (low adj1 calorie*) or vlcd).ti,ab.
11.	((low* or reduc* or percent*) adj3 (fat* or carb*)).ti,ab.
12.	((high* or percent*) adj3 protein*).ti,ab.
13.	or/5-12
14.	exp *exercise/
15.	exp *kinesiotherapy/
16.	*sedentary lifestyle/
17.	exp *physical activity/
18.	exercise*.ti,ab.
19.	((resist* or strength or weight or intens* or fitness) adj2 (train* or program* or therap*)).ti,ab.
20.	(anaerobic* or aerobic*).ti,ab.
21.	(hiit or (interval* adj2 train*)).ti,ab.

22.	(physical* adj2 (activit* or exert* or fit or fitness or train* or therap*)).ti,ab.
23.	(sedentary or ((sit or sitting) adj3 time)).ti,ab.
24.	or/14-23
25.	exp *counseling/
26.	exp *psychotherapy/
27.	*motivation/
28.	*social support/
29.	*health program/
30.	exp *self care/
31.	(cbt or (cognit* adj2 therap*) or (behav* adj1 therap*)).ti,ab.
32.	(mbt or (mentali#ation adj based adj1 therap*)).ti,ab.
33.	(feedback or biofeedback).ti,ab.
34.	((behav* or lifestyle or life-style) adj3 (modif* or program* or therap* or change* or treatment* or interven* or adjust*)).ti,ab.
35.	((multifactor* or multifacet* or multi-facet* or multi-factor* or managed) adj2 program*).ti,ab.
36.	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
37.	((support* or advice or advise) adj3 (telephone* or internet or online or web or app or apps or program* or group*)).ti,ab.
38.	(psychotherap* or psychosocial*).ti,ab.
39.	(psycholog* adj2 intervent*).ti,ab.
40.	(self adj3 (manage* or care or motivat*)).ti,ab.
41.	(henry or motivat* or educat*).ti,ab.
42.	((famil* or parent*) adj2 (therap* or program*)).ti,ab.
43.	or/25-42
44.	13 and 24
45.	43 and (13 or 24)
46.	44 or 45
47.	4 and 46
48.	Study filters SR (0) or RCT (0)
49.	47 and 48
	See Table 14 for date parameters

1 **Cochrane search terms**

#1.	Standard population (0)
#2.	[mh exercise]
#3.	[mh "exercise therapy"]
#4.	[mh ^"sedentary lifestyle"]
#5.	exercise*:ti,ab
#6.	((resist* or strength or weight or intens* or fitness) near/2 (train* or program* or therap*)):ti,ab
#7.	(anaerobic* or aerobic*):ti,ab
#8.	(hiit or (interval* near/2 train*)):ti,ab
#9.	(physical* near/2 (activit* or exert* or fit or fitness or train* or therap*)):ti,ab
#10.	(sedentary or ((sit or sitting) near/3 time)):ti,ab
#11.	{or #2-#10}

#12.	[mh ^"weight loss"]
#13.	[mh "diet therapy"]
#14.	diet*:ti,ab
#15.	(weight near/3 (loss* or lose or reduc* or percent*)):ti,ab
#16.	(hypocaloric or (low near calorie*) or vlcd):ti,ab
#17.	((low* or reduc* or percent*) near/3 (fat* or carb*)):ti,ab
#18.	((high* or percent*) near/3 protein*):ti,ab
#19.	{or #12-#18}
#20.	[mh ^counseling]
#21.	[mh "behavior therapy"]
#22.	[mh ^motivation]
#23.	[mh ^"social support"]
#24.	[mh psychotherapy]
#25.	[mh ^"managed care programs"]
#26.	[mh ^"self care"]
#27.	(cbt or (cognit* near/2 therap*) or (behav* near therap*)):ti,ab
#28.	(mbt or ((mentalization or mentalisation) next based near therap*)):ti,ab
#29.	(feedback or biofeedback):ti,ab
#30.	((behav* or lifestyle or life-style) near/3 (modif* or program* or therap* or change* or treatment* or interven* or adjust*)):ti,ab
#31.	((multifactor* or multifacet* or multi-facet* or multi-factor* or managed) near/2 program*):ti,ab
#32.	(psycholog* or council* or counsel* or psychotherap* or psychosocial):ti,ab
#33.	((support* or advice or advise) near/3 (telephone* or internet or online or web or app or apps or program* or group*)):ti,ab
#34.	(psychotherap* or psychosocial*):ti,ab
#35.	(psycholog* near/2 intervent*):ti,ab
#36.	(self near/3 (manage* or care or motivat*)):ti,ab
#37.	(henry or motivat* or educat*):ti,ab
#38.	((famil* or parent*) near/2 (therap* or program*)):ti,ab
#39.	{or #20-#38}
#40.	#11 and #19
#41.	#11 or #19
#42.	#39 and #41
#43.	#40 or #42
#44.	#1 and #43
	See Table 14 for date parameters

Monitoring

- How often should we monitor adults, young people and children with NAFLD or NASH (with or without fibrosis) to determine risk of disease progression?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2

4.	Limit 3 to English language
5.	exp disease progression/
6.	(disease adj (progress* or development* or evolution*)).ti,ab.
7.	(progress* adj2 (slow* or stable or rapid or fast or quick*)).ti,ab.
8.	(acute adj (worse* or exacerbat*)).ti,ab.
9.	(fibrosis adj2 (worse* or exacerbat*)).ti,ab.
10.	(fibrosis adj progress*).ti,ab.
11.	or/5-10
12.	4 and 11
	See Table 14 for date parameters

Embase search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	*disease course/
6.	(disease adj (progress* or development* or evolution*)).ti,ab.
7.	(progress* adj2 (slow* or stable or rapid or fast or quick*)).ti,ab.
8.	(acute adj (worse* or exacerbat*)).ti,ab.
9.	(fibrosis adj2 (worse* or exacerbat*)).ti,ab.
10.	(fibrosis adj progress*).ti,ab.
11.	or/5-10
12.	4 and 11
	See Table 14 for date parameters

Cochrane search terms

#1.	Standard population (0)
#2.	(progress* near/2 (slow* or stable or rapid or fast or quick*)):ti,ab
#3.	MeSH descriptor: [disease progression] explode all trees
#4.	(acute next (worse* or exacerbat*)):ti,ab
#5.	(fibrosis near/2 (worse* or exacerbat*)):ti,ab
#6.	(fibrosis next progress*):ti,ab
#7.	{or #2-#6}
#8.	#1 and #7
	See Table 14 for date parameters

Risk factors

- Which risk factors for NAFLD or severe NAFLD (NASH, fibrosis) aid in the identification of people who should be investigated further?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)

3.	1 not 2
4.	Limit 3 to English language
5.	waist circumference/
6.	(waist adj (circumference or size)).ti,ab.
7.	body mass index/
8.	(((body mass or quetelet) adj ind*) or bmi).ti,ab.
9.	triglycerides/bl
10.	hypertriglyceridemia/
11.	(hypertriglyceridemia* or ((raise* or high or elevat* or increase*) adj2 triglycerid*)).ti,ab.
12.	exp hypoalphalipoproteinemias/
13.	exp lipoproteins, hdl/
14.	(hypoalphalipoproteineni* or ((hdl or ((high density or high-density or alpha or heavy) adj1 lipoprotein*)) adj2 (low or lower* or hypo or deficien*))).ti,ab.
15.	exp diabetes mellitus, type 2/
16.	(diabet* adj2 (type 2 or type2 or type ii or type two)).ti,ab.
17.	(dm2 or t2d*).ti,ab.
18.	(diabet* adj2 (noninsulin or non insulin or slow-onset or slow onset or adult-onset or adult onset)).ti,ab.
19.	exp hypertension/
20.	(hypertens* or high blood pressure*).ti,ab.
21.	metabolic syndrome x/
22.	(metabolic adj1 syndrom*).ti,ab.
23.	or/5-22
24.	4 and 23
25.	Study filters RCT (0) or RISK (0)
26.	24 and 25
	See Table 14 for date parameters

1 **Embase search terms**

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	*waist circumference/
6.	(waist adj (circumference or size)).ti,ab.
7.	*body mass/
8.	(((body mass or quetelet) adj ind*) or bmi).ti,ab.
9.	*triacylglycerol/
10.	*hypertriglyceridemia/
11.	(hypertriglyceridemia* or ((raise* or high or elevat* or increase*) adj2 triglycerid*)).ti,ab.
12.	exp *hypoalphalipoproteinemia/
13.	*high density lipoprotein/
14.	(hypoalphalipoproteineni* or ((hdl or ((high density or high-density or alpha or heavy) adj1 lipoprotein*)) adj2 (low or lower* or hypo or deficien*))).ti,ab.
15.	*non insulin dependent diabetes mellitus/
16.	(diabet* adj2 (type 2 or type2 or type ii or type two)).ti,ab.

17.	(dm2 or t2d*).ti,ab.
18.	(diabet* adj2 (noninsulin or non insulin or slow-onset or slow onset or adult-onset or adult onset)).ti,ab.
19.	exp *hypertension/
20.	(hypertens* or high blood pressure*).ti,ab.
21.	*metabolic syndrome x/
22.	(metabolic adj1 syndrom*).ti,ab.
23.	or/5-22
24.	4 and 23
25.	Study filters RCT (0) or RISK (0)
26.	24 and 25
	See Table 14 for date parameters

Cochrane search terms

#1.	Standard population (0)
#2.	[mh ^"waist circumference"]
#3.	(waist next (circumference or size)):ti,ab
#4.	[mh ^"body mass index"]
#5.	((((body next mass) or quetelet) next ind*) or bmi):ti,ab
#6.	mesh descriptor: [triglycerides] explode all trees and with qualifier(s): [blood - bl]
#7.	[mh ^hypertriglyceridemia]
#8.	(hypertriglyceridemia* or ((raise* or high or elevat* or increase*) near/2 triglycerid*)):ti,ab
#9.	[mh hypoalphalipoproteinemias]
#10.	[mh "lipoproteins, hdl"]
#11.	(hypoalphalipoproteineni* or ((hdl or (("high density" or high-density or alpha or heavy) near/1 lipoprotein*)) near/2 (low or lower* or hypo or deficien*))):ti,ab
#12.	[mh "diabetes mellitus, type 2"]
#13.	(diabet* near/2 ("type 2" or type2 or "type ii" or "type two")):ti,ab
#14.	(dm2 or t2d*):ti,ab
#15.	(diabet* near/2 (noninsulin or "non insulin" or slow-onset or "slow onset" or adult-onset or "adult onset")):ti,ab
#16.	[mh hypertension]
#17.	(hypertens* or (high next blood next pressure*)):ti,ab
#18.	{or #2-#17}
#19.	#1 and #18
#20.	[mh risk]
#21.	[mh ^prevalence]
#22.	[mh ^incidence]
#23.	(risk* or prevalence* or incidence* or predict* or associat*):ti,ab
#24.	{or #20-#23}
#25.	#19 and #24
	See Table 14 for date parameters

Alcohol

- Should people with NAFLD restrict their consumption of alcohol to below national recommended levels?

1 **Medline search terms**

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp alcoholic beverages/
6.	ethanol/
7.	ethanol.ti,ab.
8.	alcohol abstinence/
9.	alcohol drinking/
10.	(alcohol* adj3 (drink* or unit* or ingest* or beverage* or intake or consum*)).ti,ab.
11.	(alcohol* adj3 (restrict* or limit* or confin* or moderat* or abstinen* or abstain* or reduc* or modest or teetotal*)).ti,ab.
12.	or/5-11
13.	4 and 12
14.	Study filters OBS (0) or RISK (0)
15.	13 and 14
	See Table 14 for date parameters

2 **Embase search terms**

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp *alcoholic beverage/
6.	*alcohol/
7.	ethanol.ti,ab.
8.	alcohol abstinence/
9.	alcohol consumption/
10.	(alcohol* adj3 (drink* or unit* or ingest* or beverage* or intake or consum*)).ti,ab.
11.	(alcohol* adj3 (restrict* or limit* or confin* or moderat* or abstinen* or abstain* or reduc* or modest or teetotal*)).ti,ab.
12.	drinking behavior/
13.	drink* behaviour*.ti,ab.
14.	or/5-13
15.	4 and 14
16.	Study filters OBS (0) or RISK (0)
17.	15 and 16
	See Table 14 for date parameters

3 **Cochrane search terms**

#1.	Standard population (0)
#2.	MeSH descriptor: [alcoholic beverages] explode all trees
#3.	MeSH descriptor: [ethanol] this term only
#4.	ethanol:ti,ab
#5.	MeSH descriptor: [alcohol abstinence] this term only
#6.	MeSH descriptor: [alcohol drinking] this term only

#7.	(alcohol* near/3 (drink* or unit* or ingest* or beverage* or intake or consum*)):ti,ab
#8.	(alcohol* near/3 (restrict* or limit* or confin* or moderat* or abstinen* or abstain* or reduc* or modest or teetotal*)):ti,ab
#9.	{or #2-#8}
#10.	#1 and #9
#11.	MeSH descriptor: [risk] explode all trees
#12.	MeSH descriptor: [prevalence] this term only
#13.	MeSH descriptor: [incidence] this term only
#14.	(risk* or prevalence* or incidence* or predict* or associat*):ti,ab
#15.	{or #11-#14}
#16.	#10 and #15
	See Table 14 for date parameters

Pharmacological

- What is the clinical and cost-effectiveness of pharmacological interventions for adults, young people and children with NAFLD?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	*hydroxymethylglutaryl-coa reductase inhibitor/
6.	statin*.ti,ab.
7.	((hydroxymethylglutaryl-coa or hmg-coa) adj3 (reductase or inhibitor*)).ti,ab.
8.	exp *simvastatin/
9.	(simvastatin* or zocor).ti,ab.
10.	(atorvastatin* or lipitor).ti,ab.
11.	(rosuvastatin* or crestor).ti,ab.
12.	exp *pravastatin/
13.	(pravastatin* or lipostat).ti,ab.
14.	(fluvastatin* or lescol).ti,ab.
15.	or/5-14
16.	exp *angiotensin 1 receptor agonist/ or *angiotensin 2 receptor agonist/
17.	((angiotensin adj3 (receptor* adj2 (antagonist* or blocker*))) or arb or arbs).ti,ab.
18.	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel).ti,ab.
19.	(coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar).ti,ab.
20.	(exforge or telmisartan or micardis or valsartan or diovan or co-diovan or azilsartan or edarbi).ti,ab.
21.	exp *angiotensin-converting enzyme inhibitors/
22.	((ace or acei or ((angiotensin adj converting adj2 enzyme*) or ace or kininase)) adj2 (inhibit* or antagonist*)).ti,ab.
23.	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co).ti,ab.
24.	(capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril).ti,ab.
25.	(quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or

	gopten or noyada or tarka).ti,ab.
26.	(imidapril or tanatril or lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl).ti,ab.
27.	exp *alpha adrenergic receptor blocking agent/
28.	(adrenergic alpha-antagonist* or adrenergic alpha antagonist*).ti,ab.
29.	(alpha blocker* adj2 (antagonist* or receptor*)).ti,ab.
30.	(doxazosin or cardura or tamsulosin or indoramin or baratol or prazosin or hypovase or terazosin or hytrin or moxisylyte or labetalol).ti,ab.
31.	exp dipeptidyl-peptidase iv inhibitor/
32.	((dpp4 or dipeptidyl peptidase-4 or dipeptidyl peptidase 4) adj2 inhibit*).ti,ab.
33.	(januvia or eucreas or galvus or onglyza or trajenta or jentadueto).ti,ab.
34.	(komboglyze or vildagliptin or sitagliptin or linagliptin or saxagliptin or metformin).ti,ab.
35.	exp glucagon like peptide 1/
36.	((glp-1 or glucagon-like peptide 1 or glucagon like peptide 1) adj2 (receptor* or agonist*)).ti,ab.
37.	(exenatide or lixisenatide or dulaglutide or liraglutide or bydureon).ti,ab.
38.	(byetta or lyxumia or trulicity or victoza).ti,ab.
39.	exp ursodeoxycholic acid/
40.	(ursodeoxycholic acid or ursodiol or usan or ucda).ti,ab.
41.	(destolit or urdox or ursofalk or ursogal).ti,ab.
42.	exp pentoxifylline/
43.	pentoxifylline.ti,ab.
44.	(trental or pentoxil).ti,ab.
45.	(orlistat or beacita or xencial or alli or tetrahydrolipstatin).ti,ab.
46.	exp metformin/
47.	(metaformin or diagemet or competact or glucient or glucophage).ti,ab.
48.	(glidipion or actospioglitazone or pioglitazone).ti,ab.
49.	exp alpha tocopherol/
50.	(vitamin e or vit* e or alpha tocopherol).ti,ab.
51.	exp vitamin d/
52.	(vitamin d or vit* d).ti,ab.
53.	or/15-52
54.	4 and 53
55.	Study filters SR (0) or RCT (0) or OBS (0)
56.	54 and 55
	See Table 14 for date parameters

Embase search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	*hydroxymethylglutaryl coenzyme a reductase inhibitor/
6.	statin*.ti,ab.
7.	((hydroxymethylglutaryl coenzyme a or hydroxymethylglutaryl-coa or hmg-coa) adj3 reductase inhibitor*).ti,ab.
8.	exp *simvastatin/

9.	(simvastatin* or zocor).ti,ab.
10.	(atorvastatin* or lipitor).ti,ab.
11.	(rosuvastatin* or crestor).ti,ab.
12.	exp *pravastatin/
13.	(pravastatin* or lipostat).ti,ab.
14.	(fluvastatin* or lescol).ti,ab.
15.	or/5-14
16.	exp angiotensin 1 receptor antagonist/ or angiotensin 2 receptor antagonist/
17.	((angiotensin adj3 (receptor* adj2 (antagonist* or blocker*))) or arb or arbs).ti,ab.
18.	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel).ti,ab.
19.	(coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar).ti,ab.
20.	(exforge or telmisartan or micardis or valsartan or diovan or co-diovan or azilsartan or edarbi).ti,ab.
21.	exp *dipeptidyl carboxypeptidase inhibitor/
22.	dipeptidyl carboxypeptidase inhibitor.ti,ab.
23.	((ace or acei or ((angiotensin adj converting adj2 enzyme*) or ace or kininase)) adj2 (inhibit* or antagonist)).ti,ab.
24.	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co).ti,ab.
25.	(capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril).ti,ab.
26.	(quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or gopten or noyada or tarka).ti,ab.
27.	(imidapril or tanatril or lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl).ti,ab.
28.	exp *alpha adrenergic receptor blocking agent/
29.	(adrenergic alpha-antagonist* or adrenergic alpha antagonist* or alpha adrenergic receptor blocking agent).ti,ab.
30.	(alpha adrenergic* adj2 (block* or receptor* or agent)).ti,ab.
31.	(doxazosin or cardura or tamsulosin or indoramin or baratol or prazosin or hypovase or terazosin or hytrin or moxisylyte or labetalol).ti,ab.
32.	exp dipeptidyl peptidase iv inhibitor/
33.	((dpp4 or dipeptidyl peptidase-4 or dipeptidyl peptidase 4) adj2 inhibit*).ti,ab.
34.	(januvia or eucreas or galvus or onglyza or trajenta or jentadueto).ti,ab.
35.	(komboglyze or vildagliptin or sitagliptin or linagliptin or saxagliptin or metformin).ti,ab.
36.	exp glucagon like peptide 1/
37.	((glp-1 or glucagon-like peptide 1 or glucagon like peptide 1) adj2 (receptor* or agonist*)).ti,ab.
38.	(exenatide or lixisenatide or dulaglutide or liraglutide or bydureon).ti,ab.
39.	(byetta or lyxumia or trulicity or victoza).ti,ab.
40.	exp ursodeoxycholic acid/
41.	(ursodeoxycholic acid or ursodiol or usan or ucda).ti,ab.
42.	(destolit or urdox or ursofalk or ursogal).ti,ab.
43.	exp pentoxifylline/
44.	pentoxifylline.ti,ab.
45.	(trental or pentoxil).ti,ab.
46.	(orlistat or beacita or xencial or alli or tetrahydrolipstatin).ti,ab.
47.	exp metformin/

48.	(metaformin or diagemet or competact or glucient or glucophage).ti,ab.
49.	(glidipion or actospioglitazone or pioglitazone).ti,ab.
50.	exp alpha tocopherol/
51.	(vitamin e or vit* e or alpha tocopherol).ti,ab.
52.	exp vitamin d/
53.	(vitamin d or vit* d).ti,ab.
54.	or/15-53
55.	4 and 54
56.	Study filters SR (0) or RCT (0) or OBS (0)
57.	55 and 56
	See Table 14 for date parameters

1 **Cochrane search terms**

#1.	Standard population (0)
#2.	MeSH descriptor: [hydroxymethylglutaryl-coa reductase inhibitors] this term only
#3.	statin*:ti,ab
#4.	((hydroxymethylglutaryl-coa or hmg-coa) near/3 (reductase or inhibitor*)):ti,ab
#5.	MeSH descriptor: [simvastatin] explode all trees
#6.	(simvastatin* or zocor):ti,ab
#7.	(atorvastatin* or lipitor):ti,ab
#8.	(rosuvastatin* or crestor):ti,ab
#9.	MeSH descriptor: [pravastatin] explode all trees
#10.	(pravastatin* or lipostat):ti,ab
#11.	(fluvastatin* or lescol):ti,ab
#12.	{or #2-#11}
#13.	MeSH descriptor: [angiotensin ii type 1 receptor blockers] explode all trees
#14.	MeSH descriptor: [angiotensin ii type 2 receptor blockers] explode all trees
#15.	((angiotensin near/3 (receptor* near/2 (antagonist* or blocker*))) or arb or arbs):ti,ab
#16.	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel):ti,ab
#17.	(coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar):ti,ab
#18.	(exforge or telmisartan or micardis or valsartan or diovan or co-diovan or azilsartan or edarbi):ti,ab
#19.	MeSH descriptor: [angiotensin-converting enzyme inhibitors] explode all trees
#20.	((ace or acei or ((angiotensin near converting near/2 enzyme*) or ace or kininase)) near/2 (inhibit* or antagonist*)):ti,ab
#21.	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co):ti,ab
#22.	(capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril):ti,ab
#23.	(quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or gopten or noyada or tarka):ti,ab
#24.	(imidapril or tanatril or lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl):ti,ab
#25.	MeSH descriptor: [adrenergic alpha-antagonists] explode all trees
#26.	(adrenergic alpha-antagonist* or adrenergic alpha antagonist*):ti,ab
#27.	(alpha blocker* near/2 (antagonist* or receptor*)):ti,ab
#28.	(doxazosin or cardura or tamsulosin or indoramin or baratol or prazosin or hypovase or terazosin or hytrin or moxisylyte or labetalol):ti,ab

#29.	MeSH descriptor: [dipeptidyl-peptidase iv inhibitors] explode all trees
#30.	((dpp4 or dipeptidyl peptidase-4 or dipeptidyl peptidase 4) near/2 inhibit*):ti,ab
#31.	(januvia or eucreas or galvus or onglyza or trajenta or jentadueto):ti,ab
#32.	(komboglyze or vildagliptin or sitagliptin or linagliptin or saxagliptin or metformin):ti,ab
#33.	MeSH descriptor: [glucagon-like peptide 1] explode all trees
#34.	((glp-1 or glucagon-like peptide 1 or glucagon like peptide 1) near/2 (receptor* or agonist*)):ti,ab
#35.	(exenatide or lixisenatide or dulaglutide or liraglutide or bydureon):ti,ab
#36.	(byetta or lyxumia or trulicity or victoza):ti,ab
#37.	MeSH descriptor: [ursodeoxycholic acid] explode all trees
#38.	(ursodeoxycholic acid or ursodiol or usan or ucda):ti,ab
#39.	(destolit or urdox or ursofalk or ursogal):ti,ab
#40.	MeSH descriptor: [pentoxifylline] explode all trees
#41.	pentoxifylline:ti,ab
#42.	(trental or pentoxil):ti,ab
#43.	(orlistat or beacita or xencial or alli or tetrahydrolipstatin):ti,ab
#44.	MeSH descriptor: [metformin] explode all trees
#45.	(metaformin or diagemet or competact or glucient or glucophage):ti,ab
#46.	(glidipion or actospioglitazone or pioglitazone):ti,ab
#47.	MeSH descriptor: [vitamin e] explode all trees
#48.	(vitamin e or vit* e):ti,ab
#49.	MeSH descriptor: [vitamin d] explode all trees
#50.	(vitamin d or vit* d):ti,ab
#51.	{or #12-#50}
#52.	#1 and #51
	See Table 14 for date parameters

Diet

- What is the clinical and cost-effectiveness of dietary interventions for weight reduction for adults, young people and children with NAFLD compared with standard care?
- What is the clinical and cost-effectiveness of dietary modifications or supplements for adults, young people and children with NAFLD compared with standard care?

Medline search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp diet/
6.	weight loss/
7.	exp diet therapy/
8.	exp fish oils/
9.	exp dietary supplements/
10.	exp dietary fiber/
11.	diet*.ti,ab.
12.	(weight adj3 (loss* or lose or reduc* or percent*)).ti,ab.

13.	(hypocaloric or (low adj1 calorie*) or vlcd).ti,ab.
14.	((low* or reduc* or percent*) adj3 (fat* or carb*)).ti,ab.
15.	((high* or percent*) adj3 protein*).ti,ab.
16.	((n-3 or n3) adj fatty acid*).ti,ab.
17.	(omega-3 or omega3 or omega 3).ti,ab.
18.	((marine or fish) adj2 (lipid* or oil* or triglyceride*)).ti,ab.
19.	(probiotic* or yakult).ti,ab.
20.	(prebiotic* or fibre or fiber).ti,ab.
21.	(diet* adj2 supplement*).ti,ab.
22.	or/5-21
23.	4 and 22
24.	Study filters SR (0) or RCT (0) or OBS (0)
25.	23 and 24
	See Table 14 for date parameters

1 **AMED search terms**

1.	Standard population (0)
2.	Limit 1 to English language
3.	exp diet/
4.	exp diet therapy/
5.	weight loss/
6.	fish oils/
7.	fatty acids/
8.	dietary fiber/ or dietary supplements/
9.	probiotics/
10.	diet*.ti,ab.
11.	(weight adj3 (loss* or lose or reduc* or percent*)).ti,ab.
12.	(hypocaloric or (low adj1 calorie*) or vlcd).ti,ab.
13.	((low* or reduc* or percent*) adj3 (fat* or carb*)).ti,ab.
14.	((high* or percent*) adj3 protein*).ti,ab.
15.	((n-3 or n3) adj fatty acid*).ti,ab.
16.	(omega-3 or omega3 or omega 3).ti,ab.
17.	((marine or fish) adj2 (lipid* or oil* or triglyceride*)).ti,ab.
18.	(probiotic* or yakult).ti,ab.
19.	(prebiotic* or fibre or fiber).ti,ab.
20.	(diet* adj2 supplement*).ti,ab.
21.	or/3-20
22.	2 and 21
	See Table 14 for date parameters

2 **Embase search terms**

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	exp *diet/

6.	exp *diet therapy/
7.	*weight reduction/
8.	*fish oil/
9.	*omega 3 fatty acid/
10.	*probiotic agent/
11.	*dietary fiber/
12.	*prebiotic agent/
13.	diet*.ti,ab.
14.	(weight adj3 (loss* or lose or reduc* or percent*)).ti,ab.
15.	(hypocaloric or (low adj1 calorie*) or vlcd).ti,ab.
16.	((low* or reduc* or percent*) adj3 (fat* or carb*)).ti,ab.
17.	((high* or percent*) adj3 protein*).ti,ab.
18.	((n-3 or n3) adj fatty acid*).ti,ab.
19.	(omega-3 or omega3 or omega 3).ti,ab.
20.	((marine or fish) adj2 (lipid* or oil* or triglyceride*)).ti,ab.
21.	(probiotic* or yakult).ti,ab.
22.	(prebiotic* or fibre or fiber).ti,ab.
23.	(diet* adj2 supplement*).ti,ab.
24.	or/5-23
25.	4 and 24
26.	Study filters SR (0) or RCT (0) or OBS (0)
27.	25 and 26
	See Table 14 for date parameters

1 **CINAHL search terms**

S1.	Standard population (0)
S2.	Excluded study designs and publication types (0)
S3.	1 not 2
S4.	Limit 3 to English language
S5.	(MH "diet+") or (MH "diet therapy+") or (MH "weight loss") or (MH "fish oils+") or (MH "dietary supplements+") or (MH "dietary fiber") or (MH "prebiotics") or (MH "fatty acids, omega-3+")
S6.	diet*
S7.	(weight n3 (loss* or lose or reduc* or percent*))
S8.	(hypocaloric or (low n1 calorie*) or vlcd)
S9.	((low* or reduc* or percent*) n3 (fat* or carb*))
S10.	((high* or percent*) n3 protein*)
S11.	((n-3 or n3) n1 fatty acid*)
S12.	(omega-3 or omega3 or omega 3)
S13.	((marine or fish) n2 (lipid* or oil* or triglyceride*))
S14.	probiotic* or yakult
S15.	prebiotic* or fibre or fiber
S16.	diet* n2 supplement*
S17.	S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15
S18.	S4 and S17
	See Table 14 for date parameters

Cochrane search terms

#1.	Standard population (0)
#2.	[mh diet]
#3.	[mh ^"weight loss"]
#4.	[mh "diet therapy"]
#5.	[mh "fish oils"]
#6.	[mh "dietary supplements"]
#7.	[mh "dietary fiber"]
#8.	diet*:ti,ab
#9.	(weight near/3 (loss* or lose or reduc* or percent*)):ti,ab
#10.	(hypocaloric or (low near/1 calorie*) or vlcd):ti,ab
#11.	((low* or reduc* or percent*) near/3 (fat* or carb*)):ti,ab
#12.	((high* or percent*) near/3 protein*):ti,ab
#13.	((n-3 or n3) next fatty acid*):ti,ab
#14.	(omega-3 or omega3 or omega 3):ti,ab
#15.	((marine or fish) near/2 (lipid* or oil* or triglyceride*)):ti,ab
#16.	(probiotic* or yakult):ti,ab
#17.	(prebiotic* or fibre or fiber):ti,ab
#18.	(diet* near/2 supplement*):ti,ab
#19.	{or #2-#18}
#20.	#1 and #19
	See Table 14 for date parameters

Health economics search

Health economic reviews

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Medline and Embase search terms

1.	Standard population (0)
2.	Excluded study designs and publication types (0)
3.	1 not 2
4.	Limit 3 to English language
5.	Study design filter HE (0)
6.	4 and 5
	See Table 14 for date parameters

CRD search terms

#1.	MeSH descriptor fatty liver explode all trees in NHSEED,HTA
#2.	MeSH descriptor non-alcoholic fatty liver disease in NHSEED,HTA
#3.	(((fatty or fat or steato*) adj3 (liver* or hepat*))) in NHSEED, HTA
#4.	(steatohepat*) in NHSEED, HTA
#5.	((visceral adj2 steato*)) in NHSEED, HTA
#6.	(nafl* or nash) in NHSEED, HTA

#7.	(#1 or #2 or #3 or #4 or #5 or #6) in NHSEED, HTA from 2014 to 2015
	See Table 14 for date parameters

HEED search terms

1.	ax=fatty or fat or steato*
2.	ax=liver* or hepat*
3.	cs=1 and 2
4.	ax=steatohepat*
5.	ax=visceral and steato*
6.	ax=nafl* or nash
7.	cs=3 or 4 or 5 or 6
	Date parameters: Inception to 13 June 2014

Quality of life reviews

Quality of life searches were conducted in Medline and Embase only. The populations for cirrhosis and NAFLD were combined for this search.

Medline search terms

1.	fatty liver/
2.	non-alcoholic fatty liver disease/
3.	(((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
4.	(nafl* or nash).ti,ab.
5.	or/1-4
6.	Excluded study designs and publication types (0)
7.	5 not 6
8.	Study filter QOL (0)
9.	7 and 8
10.	Limit 9 to English language & date parameters: 1946 to 27 August 2015
11.	exp liver cirrhosis/
12.	fibrosis/ and liver/
13.	(((liver* or hepat*) adj5 fibro*) or cirrho*).ti,ab.
14.	or/11-13
15.	ascites/
16.	ascit*.ti,ab.
17.	or/15-16
18.	14 or 17
19.	18 not 6
20.	19 and 8
21.	Limit 20 to English language & date parameters: 1946 to 13 June 2014
22.	10 or 21

Embase search terms

1.	nonalcoholic fatty liver/
2.	(((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
3.	(nafl* or nash).ti,ab.

4.	or/1-3
5.	Excluded study designs and publication types (0)
6.	4 not 5
7.	Study filter QOL (A.3.7)
8.	6 and 7
9.	Limit 8 to English language & date parameters: 1980 to 27 August 2015
10.	exp liver cirrhosis/
11.	fibrosis/ and liver/
12.	(((liver* or hepat*) adj5 fibro*) or cirrho*).ti,ab.
13.	or/10-12
14.	exp *ascites/
15.	ascit*.ti,ab.
16.	or/15-15
17.	13 or 16
18.	17 not 5
19.	18 and 7
20.	Limit 20 to English language & date parameters: 1946 to 13 June 2014
21.	9 or 20

Economic modelling

Economic modelling searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA

Medline search terms

1.	exp *liver diseases/
2.	(liver* or hepat* or steatohepat* or cirrho*).ti.
3.	or/1-2
4.	Excluded study designs and publication types (0)
5.	3 not 4
6.	Study design filter MOD (0)
7.	5 and 6
8.	Limit 7 to English language
	Date parameters: 1946 to 27 August 2015

Embase search terms

1.	exp *liver disease/
2.	(liver* or hepat* or steatohepat* or cirrho*).ti.
3.	or/1-2
4.	Excluded study designs and publication types (0)
5.	3 not 4
6.	Study design filter MOD (0)
7.	5 and 6
8.	Limit 7 to English language
	Date parameters: 1980 to 27 August 2015

CRD search terms

#1.	MeSH descriptor liver diseases explode all trees in NHSEED,HTA
#2.	(liver* or hepat* or steatohepat* or cirrho*):ti in NHSEED, HTA
#3.	#1 or #2
#4.	MeSH descriptor models, economic explode all trees in NHSEED,HTA
#5.	MeSH descriptor models, theoretical in NHSEED,HTA
#6.	MeSH descriptor models, organizational in NHSEED,HTA
#7.	MeSH descriptor markov chains in NHSEED,HTA
#8.	MeSH descriptor monte carlo method in NHSEED,HTA
#9.	MeSH descriptor decision theory explode all trees in NHSEED,HTA
#10.	(markov* or monte carlo) or (econom* model*) in NHSEED, HTA
#11.	((decision* adj2 (tree* or analy* or model*))) in NHSEED, HTA
#12.	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13.	#3 and #12
	Date parameters: Inception to 27 August 2015

1 **HEED search terms**

1.	ti=liver* or hepat* or steatohepat* or cirrho*
2.	ax=model* or markov or monte carlo
3.	cs=1 and 2
	Date parameters: Inception to 27 August 2014

2

Appendix H: Clinical evidence tables

H.1 Risk factors for NAFLD

Reference	Hamabe 2011[384]
Study type and analysis	Retrospective cohort study. 10 year follow-up (retrospective as looked at data already collected in 1998 and 2008). Logistic regression analysis
Number of participants and characteristics	N=2029 recruited. N= 1560 of these did not have NAFLD at baseline and were included in the analysis. Inclusion criteria Patients with a complete medical health check-up in 1998 and 2008. Exclusion criteria Positive for HepB and HepC. People who drank >20g/day of ethanol. Patient characteristics For non-NAFLD pts at baseline: age mean 51.1 (SD 9.3). 49.5% women. 21%. BMI ≥25 kg/m2 16.1%. Hypertension 27.1%. Dyslipidaemia 13.8%, light alcohol drinker 58.0%. Study population Conducted in Japan. People with a complete medical health check-up at a healthcare centre in both 1998 and 2008. NAFLD diagnosed by ultrasound and confirmed by an independent specialist.
Prognostic variable(s)	Key risk factors: age and hypertension
Confounders OR stratification strategy	All continuous variables considered in the study*: age, obesity, hypertension, dyslipidaemia, dysglycaemia, gender, cigarette smoking, light alcohol intake. *Definitions: obesity = BMI ≥25 kg/m2; Hypertension = SBP ≥130 mmHg/DBP≥85 mmHg; dyslipidaemia = triglycerides ≥150 mg/dl, HDL <40 IU/L, or those undergoing medical Tx of dyslipidaemia; dysglycaemia (including diabetes) = triglycerides ≥150 mg/dL; light alcohol drinkers = ≤20 g/day.
Outcomes and effect sizes	17.1% (n=266) pts developed NASH at follow-up Association between baseline variables and the development of NAFLD– OR (95% CI):

Reference	Hamabe 2011[384]
	Age: 0.95 (0.94 to 0.97) Hypertension: 0.90 (0.64 to 1.27) Metabolic syndrome (including 3 or 4 of the risk factors: obesity, hypertension, dyslipidaemia and dysglycemia): 2.99 (1.62-5.5)
Comments	High risk of bias for all outcomes

Reference	Kim 2014C[514]
Study type and analysis	Prospective cohort study. Mean 28.7 months (SD 13.2) follow-up. Logistic regression analysis
Number of participants and characteristics	N=2307 recruited. N=1154 of these did not have NAFLD at baseline and were included in the analysis. Inclusion criteria Pts in a medical check-up programme. Exclusion criteria Positive hepB or hepC. Alcohol consumption >20 g/day. Know liver disease due to another aetiology. Taking medication for diabetes, HT, and hyperlipidaemia. Patient characteristics For non-NAFLD pts at baseline: age mean 52.1. 34.4% women. BMI mean 22.5 kg/m2. HDL-c 53.8%. Study population Conducted in Korea. People participating in 2 subsequent medical check-up programmes. NAFLD diagnosed by ultrasound.
Prognostic variable(s)	Key risk factors: age, BMI, blood pressure, HDL, triglycerides, weight difference.
Confounders OR stratification strategy	For the MV analysis - all variables considered in the study: age, BMI, MS, weight difference, gender. For the model – all variables considered in the study: age, baseline BMI, weight difference, blood pressure, HDL, triglycerides, fasting blood sugar, gender. *Definitions: obesity was defined as BMI ≥25 kg/m2.
Outcomes and	17.2% (n=199) pts without NAFLD at baseline developed NAFLD at follow-up

Reference	Kim 2014C[514]
effect sizes	Non-obese pts – association* between baseline variables and the development of NAFLD - OR (95% CI): Age: 1.03 (1.02 to 1.04) BMI: 1.50 (1.16 to 1.30) Obese pts – association* between baseline variables and the development of NAFLD - OR (95% CI): Age: 1.02 (1.00 to 1.03) BMI: 1.09 (0.98 to 1.23) MODEL** in non-obese pts – association between baseline variables and the development of NAFLD - OR (95% CI): Blood pressure ≥130/85 mmHg: 1.16 (0.83 to 1.60) Triglycerides ≥150 mg/dl: 1.54 (1.10 to 2.14) MODEL** in pts – association between baseline variables and the development of NAFLD - OR (95% CI): Blood pressure ≥130/85 mmHg: 1.19 (0.86 to 1.63) Triglycerides ≥150 mg/dl: 1.29 (0.91 to 1.83) *adjusted for age, BMI, MS, weight difference, gender. **adjusted for age, baseline BMI, weight difference, blood pressure, HDL, triglycerides, fasting blood sugar, gender.
Comments	High risk of bias for all outcomes – does not mention blinding

Reference	Lee 2010[570]
Study type and analysis	Prospective cohort study. 1 year follow-up. Cox proportional hazards regression analysis
Number of participants and characteristics	N=1705 (healthy pts that had 2 evaluations ≥1 year apart) were included in the analysis. Inclusion criteria Adults aged 20 years or more. Visited Center of Health Promotion in 2004 to have health examinations, and had at least 2 evaluations at least 1 year after baseline examination. Exclusion criteria Excessive alcohol consumption ≥20 g/day. Abnormal level of GGT and ALT. Positive seromarklers for hepB or C. Biliary disease. Liver cirrhosis. Malignant disease.

Reference	Lee 2010[570]
	Patient characteristics Healthy pts (without hepatic steatosis) at baseline: age mean 43.6 (SD 8.5). 751 women. BMI ≥25 kg/m2 22.6%. BP ≥130/85 mmHg 19.8%. triglycerides ≥150mg/dl 11.7%. HDL-c <40 (men) and <50 (women) mg/dl 21.9%. Study population Conducted in Korea. People participating in health examinations in 2004 at a centre of health promotion in a Korean University. NAFLD diagnosed by ultrasound.
Prognostic variable(s)	Key risk factors: BMI ≥25 kg/m2, blood pressure ≥130/85 mmHg, triglycerides ≥150mg/dl, HDL-c <40 (men) and <50 (women) mg/dl.
Confounders OR stratification strategy	All study variables looked at as prognostic factors were: BMI ≥25 kg/m2, blood pressure ≥130/85 mmHg, triglycerides ≥150mg/dl, HDL-c <40 (men) and <50 (women) mg/dl, fasting glucose ≥100 mg/dl2. *Definitions: obesity was defined as BMI ≥25 kg/m2.
Outcomes and effect sizes	13.3% (n=226) pts without NAFLD at baseline developed NAFLD at follow-up Association between baseline variables and the development of NAFLD - HR (95% CI): BMI ≥25 kg/m2: 2.46 (1.88 to 3.22) Blood pressure ≥130/85 mmHg: 0.99 (0.72 to 1.34) Triglycerides ≥150 mg/dl: 2.10 (1.52 to 2.89) HDL-c (M <40, F <50 md/dl): 1.23 (0.91 to 2.22) Metabolic syndrome (3-5 components at baseline): 5.91 (3.93-8.89)
Comments	Low risk of bias for all outcomes

Reference	Speliotes 2010A[908] FRAMINGHAM HEART STUDY DATA
Study type and analysis	Prospective cohort study. UNCLEAR EXACT follow-up time. Multivariate regression analysis
Number of participants and characteristics	N=3529 recruited (n=1418 from the Offspring cohort, and n=2111 from the Third generation cohort). N=2509 were tested for NAFLD (tomography scan) and had follow-up data, and so were included in the analysis. Inclusion criteria

Reference	Speliotes 2010A[908] FRAMINGHAM HEART STUDY DATA
	Framingham participants. Favoured individuals who still resided in the greater New England area and included 755 families. Age≥35 years (men) and ≥40 years (women). Exclusion criteria Pregnant women. Weight >160kg. Un-interpretable tomography scans for fatty liver. Did not attend Offspring examination 7. Excessive alcohol drinking (>7 drinks/week for men or >14 drinks/week for women). Missing covariate profile. Patient characteristics For all pts at baseline: age mean 51 years. 51% women. BMI mean 27.6 kg/m2. Waist circumference mean 96.5 (SD 14.3) cm. HDL-c mean 52.5 (SD 15.8) mg/dl. Triglycerides median 103 (IQR71-155) mg/dl. HOMA IR median 2.63 (IQR 2.11 – 3.54). Type 2 diabetes n=173 (6.7%). Obesity (BMI ≥30) n=685 (26.5%). Study population Conducted in USA. People from the Offspring and Third generation cohorts participating in the Framingham study. NAFLD diagnosed by multidetector computed tomography scan (liver phantom ratio).
Prognostic variable(s)	Key risk factors*: Dichotomous: diabetes, hypertension, metabolic syndrome Continuous: triglycerides, NOTE: BMI and waist circumference were assessed but the analysis for these only adjusted for 2 of our pre-specified confounders. *definitions: diabetes = fasting plasma glucose ≥126 mg/dl or Tx with insulin or hypoglycaemic agent. Hypertension (HT) = SBP ≥140/DBP ≥90 mmHg or on anti-HT medication. Obesity =BMI ≥30 kg/m2.
Confounders OR stratification strategy	All study variables looked at were: age, BMI, waist circumference, gender, alcoholic drinks/week, menopausal status, HRT, smoking, VAT (visceral adipose tissue).
Outcomes and effect sizes	17% patients had NAFLD at follow-up Association between baseline variables and the development of NAFLD, dichotomous outcomes- OR (95% CI): Triglycerides: 1.25 (1.19-1.32), p<0.001 Hypertension: 1.52 (1.17 to 1.97), p=0.002 Diabetes: 1.64 (1.11 to 2.41) Metabolic syndrome: 1.95 (1.48 to 2.56)

Reference	Speliotes 2010A[908] FRAMINGHAM HEART STUDY DATA
Comments	High risk of bias for all outcomes – does not mention blinding

Reference	Sung 2012[931]
Study type and analysis	Prospective cohort study. Mean 4.37 years follow-up. Logistic regression analysis
Number of participants and characteristics	N=3577 recruited. N=2589 of these did not have NAFLD at baseline and were included in the analysis. Inclusion criteria E that had occupational health check with data collected for liver by ultrasounds and other relevant variables. People without NAFLD at baseline were only included if they had a further ultrasound at follow-up. Exclusion criteria Positive markers for hep B or C. Excessive alcohol consumption (>20 g/day). Patient characteristics For non-NAFLD pts at baseline: age mean 42.6 (SD 8.5). 49.6% women. BMI mean 22.9 (SD 2.6) kg/m2. Waist circumference mean 77.0 (SD 8.4)cm. SBP mean 115.2 (SD 13.8) mmHg. DBP mean 74.6 (SD 9.9) mmHg. Triglyceride median 1.10 (IQR 0.8 – 1.51) mmol/l. HDL-c mmol/l mean 1.54 (SD 0.30) mmol/l. HOMA-IR mean 1.95 (SD 0.69). Study population Conducted in Korea. Employees who had an occupational health check. NAFLD diagnosed by ultrasound and blood tests for liver function (ALT).
Prognostic variable(s)	Key risk factors: age, triglycerides, HDL-c, waist circumference, blood pressure (DBP).
Confounders OR stratification strategy	All study variables looked at were: age, triglycerides, HDL-c, waist circumference, blood pressure (DBP), gender, glucose, insulin, hsCRP, ALT, platelets, smoking.
Outcomes and effect sizes	16.6% (n=430) pts without NAFLD at baseline developed NAFLD at follow-up Association between baseline variables and the development of NAFLD - OR (95% CI): Age: 0.99 (0.98 to 1.00), p=0.176

Reference	Sung 2012[931]
	Triglycerides (per mmol/l increase): 1.38 (1.18 to 1.61), p<0.0001 HDL-c (per mmol/l increase): 0.82 (0.55 to 1.24), p=0.345 Waist circumference (per cm increase): 1.08 (1.06 to 1.10), p<0.0001 DBP: 1.00 (0.99 to 1.02), p=0.656
Comments	High risk of bias for all outcomes – does not mention blinding

Reference	Xu 2013B[1051]
Study type and analysis	Prospective cohort study. 5 year follow-up. Cox proportional hazards regression analysis
Number of participants and characteristics	N=6905 recruited. N=6403 of these did not have NAFLD at baseline. N=5562 had follow-up data and were included in the analysis. Inclusion criteria Non-obese employees from a chemical company in China. Attended health examination during 2006. Exclusion criteria Excessive alcohol consumption (>140 g/week for men, and >70g/week for women). History of viral hepatitis. Autoimmune hepatitis. Other known causes of liver disease. BMI ≥25 kg/mg2 . Taking hepatoxic medications, anti-hypertensives, anti-diabetics, lipi-lowering agents, or hyperuricaemic agents. Patient characteristics For non-NAFLD pts at baseline: age mean 43.0 (SD 12.5). 3952 women. BMI mean 21.5 (SD 2.0) kg/m2. Waist circumference mean 74.8 (SD 7.1) cm. SBP mean 117.7 (SD 14.4) mmHg. DBP mean 74.4 (SD 8.9) mmHg. HDL-c median 1.30 (IQR 1.09 – 1.60). Study population Conducted in China. People participating in medical check-up programmes. NAFLD diagnosed by ultrasound and the exclusion of other known etiology of chronic liver disease.
Prognostic variable(s)	Key risk factors: age, BMI, waist circumference, blood pressure, triglycerides, HDL-c.
Confounders OR	For the MV analysis – unclear which variables were adjusted for. All study variables looked at as prognostic factors were: age, gender, BMI, waist

Reference	Xu 2013B[1051]
stratification strategy	circumference, blood pressure, triglycerides, HDL-c, gender, γ-glutamyltransferase, total cholesterol, LDL-c, Fasting plasma gluco.0se, serum uric acid, direct bilirubin, indirect bilirubin, haemoglobin, platelet count.
Outcomes and effect sizes	8.9% (n=494) pts without NAFLD at baseline developed NAFLD at follow-up Association between baseline variables and the development of NAFLD - HR (95% CI): Age: 0.98 (0.97 to 0.99), p<0.001 BMI: 1.22 (1.13 to 1.32), p<0.001 Waist circumference: 1.08 (1.06 to 1.10), p<0.001 SBP: 1.00 (0.99 to 1.01), p=0.951 DBP: 1.01 (1.00 to 1.02), p=0.207 Triglycerides: 1.21 (1.07 to 1.37), p=0.002 HDL-c: 0.57 (0.34 to 0.96), p=0.035
Comments	Low risk of bias for all outcomes

H.2 Diagnosis of NAFLD

Study	Borman 2013[137]
Study type	Prospective validation study
Number of studies (number of participants)	1 (n=250)
Countries and Settings	Five Canadian hepatology centres
Funding	Study supported by Echosens (Paris, France).
Duration of study	July 2009 and July 2010.
Age, gender, ethnicity	Median age (IQR): 50 years (43-57). 65% Male. Ethnicity NR
Patient characteristics	Adults (≥18 years) with chronic liver disease of any etiology and a BMI ≥28kg/m^2 who had undergone liver biopsy within 6 months or were scheduled to undergo biopsy within 1 month. Exclusion criteria: BMI ≤28 kg/m^2, previous liver transplant, known malignancy or other terminal disease, refusal to undergo biopsy, missing lab data for FLI calculation. Liver disease aetiology: 40% viral hepatitis, 48% NAFLD, 12% other.
Index test	Fatty liver index (FLI) Calculation: {[*e* 0.953*ln(triglycerides, mg/dL) + 0.139*(BMI, kg/m2) + 0.718*ln(GGT, U/L) + 0.053*ln(waist circumference, cm) – 15.745)] / [1 + (*e* 0.953*ln(triglycerides, mg/dL) + 0.139*(BMI, kg/m2) + 0.718*ln(GGT, U/L) + 0.053*ln(waist circumference, cm) – 15.745)]} x 100 Accuracy of FLI at optimal thresholds defined by the maximal sum of sensitivity and specificity - 79
Reference standard	Liver biopsy, obtained under ultrasound guidance, were fixed, paraffin embedded, and stained with at least hematoxylin and eosin and Masson's trichrome. Two experiences hepatologists analysed biopsy specimens independently without knowledge of clinical data. Steatosis was assessed as the percentage of hepatocytes containing lipid droplets and categorised according to NAFLD activity score (NAS) S0 <5%, S1 5-33%, S2 34-66%, and S3 >66%
Target condition	Steatosis ≥ 5%

Study	Borman 2013[137]
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 156 FP 26 FN 37 TN 28 Sensitivity 81% Specificity 49% PPV 84% NPV 43% Area under the curve 0.67 (0.59-0.76) Author reported diagnostic accuracy for sub-group of NAFLD patients (not enough raw data to calculate 2x2 table): sensitivity 86%, specificity 50%, PPV 96%, NPV 20%, AUROC 0.68 (0.43-0.94) General limitations according to QUADAS II: Index test threshold not pre-defined, unclear timing between index test and reference standard, unclear if index test interpreted without knowledge of reference standard.	

Study	Chiang 2014[201]
Study type	Prospective study
Number of studies (number of participants	1 (n=63)
Countries and Settings	Taiwan
Funding	Supported by grants from the Chang Gung Memorial Hospital and Chang Gung Medical Foundation Institutional Review Board. GE Healthcare provided technical support.
Duration of study	Unclear – begins March 2013
Age, gender, ethnicity	Mean age (range): 30 (18-47), 46% Male. Ethnicity NR

Study	Chiang 2014[201]
Patient characteristics	Living donors with complete pre-transplant MRI evaluation and liver biopsy results.
Index test	MR IDEAL IQ Performed on a 1.5-T MR scanner. A multiecho 3D SPGR IDEAL sequence with fly-back gradients were employed for evaluation of liver steatosis. IDEAL IQ technique is a T1-independent, T2*-corrected chemical shift-based fat-water separation method with multipeak fat spectral monitoring. To estimate hepatic fat fraction, the signal intensity from regions of interest in liver were calculated in an IDEAL fat fraction map image. All measurements were performed by two experiences radiologists. Cut-off 3.42
Reference standard	Liver biopsy Zero-hour biopsies obtained by wedge resection during surgery. Histologic grading of macrovesicular steatosis was performed by two independent radiologists. Hepatic steatosis graded as a quantitative evaluation of percentage of hepatocytes: <5%. 5-10%, 11-15%, >15%.
Target condition	Macrovesicular steatosis ≥ 5%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 15 FP 11 FN 0 TN 37 Sensitivity 100% Specificity 77.1% Area under the curve 0.98 (0.00-1.00) General limitations according to QUADAS II: Unclear if index test threshold was pre-defined, unclear timing between index test and reference standard, unclear if index test interpreted without knowledge of reference standard.	

Study	Chon 2014[205]
Study type	Prospective study

Study	Chon 2014[205]
Number of studies (number of participants	1 (n=135)
Countries and Settings	Single centre, University College Hospital, Korea
Funding	None reported
Duration of study	Between November 2011 and July 2012
Age, gender, ethnicity	Mean age (range): 51 years (18-63). Male 64.4%. Ethnicity NR
Patient characteristics	Patients receiving liver biopsy and CAP for diagnoses of chronic liver diseases or decisions to treat. No previous or current drugs for hyperlipidaemia, insulin sensitisers, antioxidants, or ursodeoxycholic acid, antivral treatments using nucleot(s)ide analogues or interferon/ribavirin and immunosuppressive agents. Ten patients excluded for unreliable liver stiffness values, liver stiffness measurement failure, non-interpretable biopsies, and the presence of hepatic malignancy. Average BMI (range): 24.4 kg/m^2 (14.3-33.5) Liver disease aetiology: NAFLD 41.5%, Hepatitis B 34.8%, Hepatitis C 8.9%, other 14.8%
Index test	CAP Measures ultrasonic attenuations at 3.5 MHz using signals acquired by FibroScan. The CAP is calculated only when liver stiffness is valid for the same signals, ensuring that one obtains liver ultrasonic attenuation simultaneously and in the same volume of liver parenchyma as liver stiffness measurement. Final CAP was the median of individual CAP values using the same valid measurements. In 91.8% of cases CAP measurement was performed at the same site as biopsy to reduce potential bias. Optimal CAP cut-off values for maximum sensitivity and specificity: steatosis ≥5% 250 dB/m and ≥34% 299 dB/m
Reference standard	Ultrasound-guided liver biopsy performed same day as CAP. Specimens were fixed in formalin and embedded in paraffin, then 4-µm thick sections subjected to haematoxylin-eosin and Masson's trichrome staining. All liver samples evaluated by an experienced hepatopathologist who had no access to clinical data. Steatosis of any aetiology assessed as the percentage of hepatocytes containing lipid droplets following NAFLD activity score (NAS) S0 ≤5%, S1 5-33%, S2 34-66%, and S3 ≥66%
Target condition	Steatosis ≥5% Steatosis ≥34%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence	Results: 2x2 table calculated using author-reported sens, spec and study prevalence

Study	Chon 2014[205]	
	Steatosis ≥5%	**Steatosis ≥34%**
	TP 68 FP 2 FN 25 TN 40 Sensitivity 73% Specificity 95% PPV 97% NPV 61.5% Area under the curve 0.885 (0.818-0.933)	TP 28 FP 14 FN 6 TN 87 Sensitivity 82% Specificity 86% PPV 66.7% NPV 93.5% Area under the curve 0.894 (0.829-0.940)
General limitations according to QUADAS II: Index test threshold not pre-defined.		

Study	Dasarathy 2009[236]
Study type	Prospective study
Number of studies (number of participants	1 (n=73)
Countries and Settings	Single centre Gastroenterology division of an urban medical centre, USA
Funding	Part funded by an NIH Institutes of Health grant
Duration of study	Unclear
Age, gender, ethnicity	Mean age (SD): 48 (10.7). Male 66%. Ethnicity NR
Patient characteristics	Patients undergoing elective liver biopsy for clinical indications of abnormal liver function or clinical suspicion of liver disease. Mean BMI (SD): 30.6 kg/m^2 (6.9) Liver disease aetiology: NAFLD 28.8%, Hepatitis B 9.6%, Hepatitis C 52.1%, other 9.6%
Index test	Real time ultrasound performed using a Sonosite Micromaxx. Ultrasound performed just prior to biopsy by a single investigator masked to the clinical diagnosis. Results initially categorised into the presence or absence of hepatic

Study	Dasarathy 2009[236]
	steatosis. An attempt was also made to differentiate the degree of steatosis during ultrasound interpretation into no fat, mild fatty liver and severe fatty liver. Predefined criteria for determining the severity of hepatic steatosis included the presence of bright echoes or increased hepatorenal contrast indicative of mild steatosis, presence of both bright echoes and increased hepatorenal contrast as well as vessel blurring indicative of moderate steatosis and severe steatosis was considered to be present when in addition to the criteria for moderate steatosis there was evidence of posterior bean attenuation and non-visualisation of the diaphragm.
Reference standard	Percutaneous liver biopsy performed using an 18G Bard Monopty biopsy gun with a single pass by the percutaneous route in the right lower intercostal space. Hematoxylin and eosin stained slides were used for assessing the type and degree of steatosis. Biopsy reviewed by a pathologist masked to clinical indication or sonographic findings. Severity of hepatic steatosis was classified as mild if the area of involvement by fat was 5-35%, moderate when >35-66% and severe when >65%
Target condition	Macrovesicular fat ≥5%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 38 FP 0 FN 8 TN 27 Sensitivity 83% Specificity 100% Area under the curve 0.912 (0.847-0.977) General limitations according to QUADAS II: No serious limitations – adequate selection, index and reference test flow and timing.	

Study	De Lédinghen 2012[242]
Study type	Prospective study
Number of studies (number of participants	1 (n=112)

Study	De Lédinghen 2012[242]
Countries and Settings	Single-centre Hospital Hepatology unit, France
Funding	Study sponsored by Echosens
Duration of study	Between June 2009 and July 2010
Age, gender, ethnicity	Mean age (SD): 53.8 years (12.2). Male 48.3%. Ethnicity NR
Patient characteristics	Exclusions based on unreliable liver stiffness measurements or liver biopsies unsuitable for staging. Aetiologies for chronic liver disease: NAFLD 25%, chronic hepatitis C 36%, alcoholic liver disease 5.3%, other 34%
Index test	CAP, FLI, Steatotest Steatotest includes alpha2-macroglobin, apolipoprotein A1, haptoglobin, total bilirubin, AST, ALT, GGT, fasting glucose, total cholesterol, tryglicerides, weight and height, agjusted for age and gender. Scores range from 0 to 1.00. Steatotest score computed on the Biopredictive website. FLI calculated according to the formula: {[*e* 0.953*ln(triglycerides, mg/dL) + 0.139*(BMI, kg/m2) + 0.718*ln(GGT, U/L) + 0.053*ln(waist circumference, cm) – 15.745)] / [1 + (*e* 0.953*ln(triglycerides, mg/dL) + 0.139*(BMI, kg/m2) + 0.718*ln(GGT, U/L) + 0.053*ln(waist circumference, cm) – 15.745)]} x 100 CAP performed using FibroScan by experienced operators. All patients measured using the 3.5 MHz standard M probe. CAP computed only when associated liver stiffness measurement was valid and using same signals as the one used to measure liver stiffness (same volume of liver parenchyma, namely between 25-65mm). The final CAP was the median of individual CAP values. Cut-off values were computed for maximising accuracy. CAP 311 dB/m, FLI 0.94, Steatotest 93.9
Reference standard	Liver biopsy performed by senior operators according to the Menghini technique using a 1.6mm diameter needle. Specimens were fixed in formalin and paraffin embedded. 4 mm thick sections were stained with haematoxylin-eosin-safran, Masson's trichromic stain for collagen, Perl's stain for iron and Gordon Sweets reticulin stain. All liver biopsies were analysed by the same experienced heparopathologisr who was blinded to CAP results. Steatosis was graded by visual assessment as S0 <10% hepatocytes, S1 11-33%, S2 34-66%, S3 67-100%
Target condition	Steatosis ≥34%

Study	De Lédinghen 2012[242]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CAP** TP 19 FP 5 FN 14 TN 74 Sensitivity 57% Specificity 94% PPV 81% NPV 83% Area under the curve 0.86 (0.78-0.95)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FLI** TP 9 FP 3 FN 24 TN 76 Sensitivity 27% Specificity 96% PPV 73% NPV 74% Area under the curve 0.71 (0.59-0.83)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatotest** TP 3 FP 1 FN 30 TN 78 Sensitivity 10% Specificity 99% PPV 75% NPV 71% Area under the curve 0.73 (0.61-0.84)	
General limitations according to QUADAS II: Index test thresholds not pre-defined and unclear if interpreted by someone blinded to biopsy results. Author calculated PPV and NPV slightly off when calculate 2x2 data according to author-reported prevalence and sens, spec.			

Study	De Moura Almeida 2008[244]
Study type	Prospective study
Number of studies (number of participants	1 (n=105)
Countries and Settings	Brazil
Funding	Supported by PAPES/CNPq n° 400267/2006-3
Duration of study	From October 2004 to May 2005.
Age, gender, ethnicity	Mean age (SD): 37.2 years (10.6). Male 25%. Ethnicity NR
Patient characteristics	Obese adults (>18 years) undergoing bariatric surgery (BMI >40 kg/m^2 or >35 kg/m^2 if associated with other conditions such as hypertension, diabetes, dyslipidaemia or sleep apnoea).

Study	De Moura Almeida 2008[244]
	Patients with alcohol intake >20 g/d or those with other chronic liver diseases (hep B or C infection, haemochromatosis, autoimmune hepatitis, Wilson's disease, primary biliary cirrhosis, α-1 antitrypsin-deficiency) were excluded (n=17).
Index test	Ultrasound as part of routine preoperative assessment carried out by different radiologists. Definition of steatosis based on diagnosis criteria such as diffuse hyperechoic echotexture, deep attenuation, increased liver echotexture compared with the kidney and vascular blurring.
Reference standard	Intraoperative wedge biopsy. All samples processed and examined by single pathologist using haematoxylin-eosin stain. Hepatic steatosis graded according to the involved hepatocytes: Grade I: 5-25%, grade II: 25-50%, grade III: 50-75%, grade IV: >75%.
Target condition	Steatosis ≥5%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 61 FP 1 FN 33 TN 10 Sensitivity 65% Specificity 91% PPV 98% NPV 23% Area under the curve NR General limitations according to QUADAS II: Unclear if index test interpreted without knowledge of reference standard and although index test threshold may be predefined it is "explained elsewhere" and not detailed in the current paper.	

Study	Fedchuk 2014[295]
Study type	Retrospective analysis of medical records

Study	Fedchuk 2014[295]
Number of studies (number of participants	1 (n=324)
Countries and Settings	France
Funding	Funding received from the European Community's Seventh Framework Programme
Duration of study	Between 2000-2010
Age, gender, ethnicity	Median age (IQR): 54 years (45-60). Male 64%. Ethnicity NR
Patient characteristics	Liver biopsy's performed for clinical and/or ultrasonographic suspicion of NAFLD. Median BMI (IQR): 29 kg/m^2 (26-33) Exclusion criteria: alcohol consumption ≥30 g/day in men or ≥20 g/day in women, presence of Hep B surface antigen or anti-hepaticis C virus antibodies, genetic haemochromatosis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, alpha 1-antitrypsin deficiency, Wilson's disease, drug-induced liver disease, cardiac insufficiency or any other chronic liver disease or patients taking medications that could induce secondary NASH.
Index test	FLI, NAFLD liver fat score Calculated with clinical, anthropometric and laboratory data retrieved at the time of each liver biopsy. FLI calculated according to the formula: {[*e* 0.953*ln(triglycerides, mg/dL) + 0.139*(BMI, kg/m2) + 0.718*ln(GGT, U/L) + 0.053*ln(waist circumference, cm) – 15.745)] / [1 + (*e* 0.953*ln(triglycerides, mg/dL) + 0.139*(BMI, kg/m2) + 0.718*ln(GGT, U/L) + 0.053*ln(waist circumference, cm) – 15.745)]} x 100 NAFLD-LFS calculated according to formula: -2.89+1.18*metabolic syndrome (yes=1, no=0) + 0.45*type 2 diabetes (yes=2, no=0) + 0.15* insulin(mU/L) + 0.04* AST(U/L) – 0.94* AST/ALT Optimal cut-offs identified using the Youden index FLI 60, and 82, NAFLD-LFS 0.16.
Reference standard	Ultrasound-guided liver biopsy. Formalin-fixed, paraffin-embedded and haematoxylin & eosin and Picrosirius Hemalun stained. All graded by single pathologist blinded to clinical data and categorised according to Kleiner: none <5%, mild ≥5-33%, moderate >33-66%, and severe >66%.
Target condition	Steatosis ≥5% Steatosis >33%

Study	Fedchuk 2014[295]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FLI: Steatosis ≥5%** TP 235 FP 2 FN 74 TN 13 Sensitivity 76% Specificity 87% PPV 99% NPV 15% Area under the curve 0.83 (0.72-0.91)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD-LFS: Steatosis ≥5%** TP 201 FP 2 FN 108 TN 13 Sensitivity 65% Specificity 87% PPV 99% NPV 11% Area under the curve 0.80(0.69-0.88)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FLI: Steatosis >33%** TP 109 FP 43 FN 75 TN 97 Sensitivity 59% Specificity 69% PPV 71% NPV 56% Area under the curve 0.65(0.59-0.71)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD-LFS: Steatosis >33%** TP 144 FP 57 FN 40 TN 83 Sensitivity 78% Specificity 59% PPV 71% NPV 67% Area under the curve 0.72(0.66-0.77)
General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection, lack of clarity around whether the steatosis biomarkers were calculated without knowledge of biopsy outcome and unclear timing of biomarker measurements with respect to reference standard (suggests some could be taken as much as six months apart).			

Study	Ferraioli 2014[303]
Study type	Cross-sectional study
Number of studies (number of participants	1 (n=109)
Countries and Settings	Single centre, Italy
Funding	FibroScan device made available by Echosens
Duration of study	From Feb 2012 to Nov 2013
Age, gender, ethnicity	Mean age (SD): 43.1 years (10.5). Male 26%. Ethnicity NR

Study	Ferraioli 2014[303]	
Patient characteristics	Patients undergoing liver biopsy for chronic viral hepatitis based on the presence of serum markets of infection with hepatitis B or C, or HIV infection and ALT levels >1.5 the upper normal limit, either persistently or intermittently. Alcohol consumption <20 g/day. Exclusions: decompensated liver cirrhosis. 50% BMI ≥25 kg/m^2	
Index test	CAP same day as liver biopsy. CAP obtained using FibroScan 502 touch with M probe. All examinations carried out by the same experienced physician. Optimal cut-offs according to ROC curve: 219 dB/m and 296 dB/m	
Reference standard	Ultrasound-assisted percutaneous liver biopsy performed by three experienced physicians using intercostal approach. A disposable 1.4mm-diameter modified Menghini needle was used. All specimens were fixed in formalin and embedded in paraffin. Specimens interpreted by single expert liver pathologist blind to CAP results but not the patient's clinical and biochemical data. Steatosis expressed as percentage of fat in the hepatocytes and graded according to Kleiner method: S0 ≤5%, S1 5-33%, S2 34-66%, and S3 ≥66%	
Target condition	Steatosis ≥5% Steatosis ≥34%	
Results: 2x2 table calculated using author-reported sens, spec, PPV and NPV as prevalence does not reflect the missing data for the six patients who were not analysed due to M-probe failure. **Steatosis ≥5%** TP 41 FP 31 FN 4 TN 33 Sensitivity 91% Specificity 52% PPV 57% NPV 89% Area under the curve 0.76 (0.67-0.84)	Results: 2x2 table calculated using author-reported sens, spec, PPV and NPV as prevalence does not reflect the missing data for the six patients who were not analysed due to M-probe failure. **Steatosis ≥34%** TP 9 FP 8 FN 6 TN 86 Sensitivity 60% Specificity 91.5% PPV 53% NPV 93.5% Area under the curve 0.82 (0.74-0.89)	

Study	Ferraioli 2014[303]
General limitations according to QUADAS II: Unclear if index test threshold was pre-defined, unclear if index test interpreted without knowledge of reference standard. Six missing cases unable to be analysed due to M probe failure are not described histologically so therefore 2x2 calculations based on author-reported accuracy measures.	

Study	Hepburn 2005[418]
Study type	Retrospective analysis of ultrasound reports
Number of studies (number of participants	1 (n=122)
Countries and Settings	Tertiary care gastroenterology clinic in a military academic medical centre, USA
Funding	None reported
Duration of study	Over a three year period
Age, gender, ethnicity	(reported separately for steatosis and no steatosis) mean age (SD): steatosis 47.9 years (10.3); no steatosis 46.3 years (10.3). Male: steatosis 63%; no steatosis 67%
Patient characteristics	Computerised records of all patients who underwent screening hepatic ultrasound with hepatitis C infection confirmed by serum HCV RNA PCR testing. Characteristics reported for 164 patients with ultrasound results but analysis only includes 122 with available biopsy specimens.
Index test	Ultrasound ALT Ultramark HDI 3000 or 5000 Ultrasound System. Ultrasound reports scored on a binomial variable. If the ultrasound report mentioned steatosis as a finding it was designated positive. If the ultrasound did not mention steatosis it was labelled negative. Equivocal studies containing phrases such as “possible steatosis” or “inflammation and steatosis” were excluded from the final analysis. Reports did not distinguish between diffuse or focal fatty liver.
Reference standard	Liver biopsies generally performed within 1-2 months of hepatic ultrasound (none included that were >6 months after ultrasound). Two pathologists retrospectively reviewed the biopsies and a percentage of steatosis was assigned to each specimen. Pathologists were blinded to ultrasound results and clinical characteristics of the patients. Compared stages of 0-2%, 2-10%, 10-30%. 30-60% and >60% as well as a binomial comparison of significant steatosis vs. not significant >30%.

Study	Hepburn 2005[418]
Target condition	Steatosis >30%
Results: 2x2 table calculated using author-reported sens, spec, PPV and NPV as prevalence only reported for 'any steatosis' (>2%) rather than steatosis >30% TP 12 FP 28 FN 8 TN 74 Sensitivity 60% Specificity 73% PPV 30% NPV 90% Area under the curve NR General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection, lack of clarity around whether the ultrasounds were interpreted without knowledge of biopsy outcome and unclear timing of ultrasound with respect to reference standard (suggests possible range of one to six months). Prevalence for stages of steatosis not reported so does not allow checking of author-reported diagnostic accuracy results.	

Study	Jun 2014[484]
Study type	Prospective study
Number of studies (number of participants	1 (n=3,855)
Countries and Settings	Medical centre, Korea
Funding	None reported
Duration of study	Feb 2001 – April 2012
Age, gender, ethnicity	Mean age (SD) 29 years (8.8). Male 66.5%. Ethnicity NR
Patient characteristics	Potential living donors undergoing percutaneous liver biopsy as part of a pre-donation workup procedure. Excluded if ≥40 g/week alcohol use, and the presence of serum hepatitis B surface antigen and hepatitis C virus

Study	Jun 2014[484]	
	antibodies as well as antibodies to HIV. Note: characteristics only reported for 1766/3859 patients who went on to become actual donors. Mean BMI 22.8 kg/m^2 (SD 2.6)	
Index test	Abdominal Doppler ultrasonography for the detection of parenchymal liver disease Steatosis was diagnosed on the basis of the presence of liver brightness and posterior attenuation with stronger echoes in the hepatic parenchyma versus the renal parenchyma, vessel blurring and narrowing of the lumina of the hepatic veins. Hepatic steatosis was also diagnosed when the difference between hepatic and splenic attenuation exceeded +10 HU on non-contrast-enhanced CT scans. Results were expressed in terms of a binary outcome: the presence or absence of hepatic steatosis. Two hepatic radiologists assessed each scan by consensus.	
Reference standard	Liver biopsy as part of routine preoperative evaluation for living donor liver transplantation. Ultrasound-guided percutaneous biopsy of the right liver lobe performed via the intercostal approach with 10-gauge needles. Two or more biopsy specimens, each approximately 1.5cm in length were obtained from every patient. For the present study, archived formalin-fixed, paraffin-embedded specimens obtained from wedge biopsies were sliced thinly and they were examined after haematoxylin and eosin staining. The extent of macovesicular and microvesicluar steatosis was quantified with a percentage scale (amount of liver parenchyma that was replaced by macro- or microvesicular lipid droplets) and a 4-grade classification was based on their sum: grade I: 5 to <15%, grade II: 15 to <30%, grade III: ≥30%.	
Target condition	Steatosis ≥5% Steatosis ≥30%	
Results: 2x2 table calculated using author-reported sens, spec, PPV and NPV as prevalence only reported for those who went on to be actual liver donors. **Steatosis ≥5%** TP 903 FP 262 FN 858 TN 1833 Sensitivity 51% Specificity 87.5% PPV 77.6% NPV 68% Area under the curve NR	Results: 2x2 table calculated using author-reported sens, spec, PPV and NPV as prevalence only reported for those who went on to be actual liver donors. **Steatosis ≥30%** TP 343 FP 818 FN 62 TN 2633 Sensitivity 85% Specificity 76% PPV 29.6% NPV 97.7% Area under the curve NR	

Study	Jun 2014[484]
General limitations according to QUADAS II: No characteristic information available for full sample size (only those who went on to become actual donors). Unclear if index test interpreted without knowledge of reference standard and unclear interval between index test and reference standard. Prevalence for stages of steatosis not reported so does not allow checking of author-reported diagnostic accuracy results.	

Study	Junior 2012[486]
Study type	Retrospective analysis of medical records
Number of studies (number of participants	1 (n=259)
Countries and Settings	Brazil
Funding	None reported
Duration of study	From January 2007 to August 2010
Age, gender, ethnicity	Mean age (range): 38.38 years (20-65). Male: 18.5%. Ethnicity NR
Patient characteristics	All records of patients submitted to bariatric surgery. Alcohol induced liver disease was excluded since one of the contraindications of bariatric surgery at the current institution is present and/or past abuse of alcohol (>30 g/day). Patients with other liver diseases such as viral hepatitis and haemochromatosis were also excluded. Mean BMI (SD): 49.84 kg/m^2 (7.44). Disease aetiology: NAFLD 92.27%
Index test	Abdominal ultrasonography was performed in all patients as our preoperative routine. No single radiologist was designated to perform the exam, but at least five different physicians performed it during the 43 months of the study.
Reference standard	Wedge liver biopsies during Roux-en-Y gastric bypass. Liver biopsies were routinely stained with haematoxylin and eosin, Masson's trichrome, and special stains for iron. Two liver pathologists examined them and determined stage of steatosis according to Brunt: Mild grade I: steatosis (predominantly macrovesicular) involving up to 66% of biopsy; Moderate grade II: steatosis of any degree; Severe grade III: panacinar steatosis.
Target condition	Steatosis >33%

Study	Junior 2012[486]
Results: 2x2 table calculated using author-reported sens, spec, PPV and NPV as prevalence only reported for any level of steatosis. TP 32 FP 48 FN 4 TN 175 Sensitivity 89.5% Specificity 78.5% PPV 41% NPV 95.5% Area under the curve NR General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection, lack of clarity around whether the ultrasounds were interpreted without knowledge of biopsy outcome and unclear timing of ultrasound with respect to reference standard. Prevalence for stages of steatosis not reported so does not allow checking of author-reported diagnostic accuracy results.	

Study	Koelblinger 2012[529]
Study type	Prospective study
Number of studies (number of participants	1 (n=35)
Countries and Settings	Single-centre, Austria
Funding	None reported
Duration of study	From March 2008 to October 2010
Age, gender, ethnicity	Male mean age (SD): 60.7 years (7.4). Female mean age (SD): 60.3 years (12.1). Male 49%. Ethnicity NR.
Patient characteristics	31/35 on neoadjuvant chemotherapy. Indication for liver resection: Colorectal metastases 31/35, cholangiocarcinoma 3/35, adenoma 1/35

Study	Koelblinger 2012[529]
Index test	3.0 T MRS of the liver within one week prior to hepatic resection Single voxel MR spectroscopic data with a volume of interest size of 30mm x 30mm x 30mm were obtained using a point resolved spatially located spectroscopic pulse (PRESS) sequenced (TE 30ms; TR 2000ms; 4 acquisitions; 2 dummy scans 1024 data points) within one breath hold (duration 12 s) with automatic shimming. The VOI was positioned in the superior and the inferior right liver lobe distant from tumor tissue and major vascular structures and the measurements were performed twice in each VOI position. One operator, who was unaware of the histopathological results, processed all spectra using the vendor's post-processing software. This included automatic phase correction based on the water and 200ms exponential filter. AUC were calculated by the software for the water and fat peaks after T1 and T2 correction using previously validated values. Optimal cut-off values where the sum of the sensitivity and specificity become largest were calculated: MRS 2.7%
Reference standard	H&E stained resection specimens. The percentage of micro- and macrovesicular steatosis was assessed by two hepatopathologists. Graded as ≥30% marked steatosis and <5% no steatosis.
Target condition	Steatosis ≥30%
Results: 2x2 table calculated using author-reported raw data TP 12 FP 3 FN 0 TN 20 Sensitivity 100% Specificity 87% PPV 80% NPV 100% Area under the curve NR General limitations according to QUADAS II: No serious limitations – adequate selection, index and reference test flow and timing.	

Study	Lassailly 2011[555]
Study type	Prospective validation cohort
Number of studies (number of participants	1 (n=288)
Countries and Settings	France
Funding	Support provided by OSEO
Duration of study	From 2006 to 2009
Age, gender, ethnicity	Mean age (SD): 41.6 years (12.8). Male 24%. Ethnicity NR
Patient characteristics	Severely obese patients referred for evaluation in view of bariatric surgery. BMI >35 mg/m^2, at least one comorbidity factor (arterial hypertension, diabetes mellitus) for at least 5 years and resistance to medical treatment, absence of medical or psychological contraindications for bariatric surgery, absence of current excessive drinking and no history of past excessive drinking for a period longer than 2 years in the past 20 years, absence of long-term consumption of hepatoxic drugs and negative screening of chronic liver diseases including negative testing for hepatitis B surface antigen and hepatitis C antibodies and no evidence of genetic haemochromatosis Mean BMI (SD): 48.6 kg/m^2 (8.9)
Index test	Steatotest Includes α2-macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, GGT, ALT, serum glucose, triglycerides, and cholesterol, adjusted for age, sex, and BMI. Scores ranged from 0 to 1.00. Predetermined conversion for steatosis grade was 0.00-0.57 for S0, greater than 0.57-0.69 for S1, and greater than 0.69-1.00 for S2-S3. Predetermined cut-offs: 0.38 and 0.69
Reference standard	Liver biopsies classified by two pathologists. Biopsies were routinely stained with hematoxylin and eosin and Masson's trichome. Graded using the NAS : S0 ≤5%, S1 5-33%, S2 34-66%, and S3 ≥66%
Target condition	Steatosis ≥5% Steatosis >33%

Study	Lassailly 2011[555]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥5%** TP 219 FP 18 FN 33 TN 18 Sensitivity 87% Specificity 50% PPV 65% NPV 35% Area under the curve NR		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis >33%** TP 58 FP 31 FN 81 TN 118 Sensitivity 42% Specificity 79% PPV 65% NPV 59% Area under the curve 0.70 (0.63-0.75)
General limitations according to QUADAS II: Unclear if Steatotest interpreted without knowledge of the reference standard. Although cut-offs are stated as predetermined no details are provided. Unclear timing between index test and reference standard.		

Study	Lee 2007[569]
Study type	Retrospective analysis of medical records
Number of studies (number of participants	1 (n=589)
Countries and Settings	Single medical centre, Korea
Funding	None reported
Duration of study	From July 2004 to September 2005
Age, gender, ethnicity	Mean age (SD): 31.1 years (9.5).Male 69%. Ethnicity NR.
Patient characteristics	Potential liver donors Excluded alcohol intake of 40 g/week or more, a history of autoimmune liver disease or other liver diseases, a positive serologic finding for hepatitis B or C virus, or AST or ALT levels exceeding 3-times the upper limit of normal.

Study	Lee 2007[569]	
	Liver aetiology: NAFLD 51.4%	
Index test	Hepatic ultrasound performed by experienced radiologists. Fatty liver was diagnosed by the presence of ultrasonographic patterns consistent with stronger echoes in the hepatic parenchyma than the renal parenchyma, posterior attenuation and vessel blurring.	
Reference standard	Ultrasound-guided percutaneous biopsies of the right lobe using 18 gauge Stericut needles. Samples were fixed in 10% formalin and stained with hematoxylin and eosin, and all pathological specimens were reviewed by expert liver pathologists. Hepatic steatosis was diagnosed when the percentage of hepatocytes showing fatty changes was ≥5% including both macro- and microvesicular steatosis. Mild steatosis 5-30%, moderate simple steatosis >30-60%, severe simple steatosis >66%	
Target condition	Steatosis ≥5% Steatosis >30%	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥5%** TP 151 FP 25 FN 152 TN 261 Sensitivity 50% Specificity 91% PPV 86% NPV 63% Area under the curve NR		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis >30%** TP 56 FP 118 FN 5 TN 410 Sensitivity 92% Specificity 78% PPV 34.5% NPV 99% Area under the curve NR
General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection, lack of clarity around whether the ultrasounds were interpreted without knowledge of biopsy outcome and unclear timing of ultrasound with respect to reference standard		

Study	Lee 2010[575]
Study type	Prospective study
Number of studies (number of participants	1 (n=161)
Countries and Settings	Single centre, Korea
Funding	Supported by a grant from Asan Institute for Life Sciences
Duration of study	Between April and October 2007
Age, gender, ethnicity	Mean age (SD): 32.2 years (9.6). Male 64%. Ethnicity NR
Patient characteristics	Applicants for living hepatic donation with criteria: absence of any documented liver disease, negative serologic findings for hepatitis B and C, AST or ALT levels below three times the upper normal limit. Exclusion criteria: abnormalities except for hepatic steatosis at the donor evaluation and those who showed uneven hepatic steatosis on ultrasound. Liver disease aetiology: NAFLD 30%
Index test	DGE-MRI, ^{1}H-MRS both performed using a 3.0 T MR imaging system. DE-MRI according to modified Dixon method. Entire liver scanned twice with breath-hold (approx. 20 s per scan) and then an index of the degree of hepatic steatosis calculated using the signal change of the liver between in-phase and opposed-phase images after correcting the T2* effect to avoid measurement error. ^{1}H-MRS performed using a point-resolved-spectoscopy sequence after automatic shimming. Signal acquisition was performed under shallow gentle free-breathing as the acquisition required 6.5min, and use d2x2x2cm^{3} voxel of interest positioned between hepatic segments V, VI, VIII, and VIII devoid of macroscopic vessels. An index of degree of hepatic steatosis was then calculated by measuring the areas of lipid (1.3pp) and water (4.7ppm) peaks after correcting t2 effect. Optimal cut-off values were where the sum of sensitivity and specificity became the largest MRI 4.0 and 6.5, MRS 2.6 and 7.7
Reference standard	Ultrasound-guided liver biopsy same day as index tests. Three radiologists performed liver biopsy using an 18 gauge needle employing a freehand technique. Biopsy specimens were obtained twice at two different sites located between hepatic segments V, VI, VIII and VIII. An experienced hepatic pathologist who was blinded to radiologic findings review histologic results. Slides were prepared with haematoxylin-eosin and Masson trichome staining. The degree of hepatic steatosis was visually assessed using a percentage scale (the amount of liver parenchyma replaced by steatotic droplets).

Study	**Lee 2010[575]**		
Target condition	Steatosis ≥5% Steatosis ≥30%		
Results: 2x2 table calculated using author-reported raw data **MRI: Steatosis ≥5%** TP 46 FP 13 FN 14 TN 88 Sensitivity 77% Specificity 87% PPV 78% NPV 86% Area under the curve 0.883 (0.823-0.928)	Results: 2x2 table calculated using author-reported raw data **MRS: Steatosis ≥5%** TP 48 FP 20 FN 12 TN 81 Sensitivity 80% Specificity 80% PPV 71% NPV 87% Area under the curve 0.849 (0.784-0.900)	Results: 2x2 table calculated using author-reported raw data **MRI: Steatosis >30%** TP 10 FP 9 FN 1 TN 141 Sensitivity 91% Specificity 94% PPV 53% NPV 99% Area under the curve 0.995 (0.967-0.999)	Results: 2x2 table calculated using author-reported raw data **MRS: Steatosis >30%** TP 8 FP 31 FN 3 TN 119 Sensitivity 73% Specificity 79% PPV 20.5% NPV 97.5% Area under the curve 0.910 (0.855-0.950)
General limitations according to QUADAS II: Index test threshold not pre-defined and unclear if interpreted without knowledge of the reference standard.			

Study	**Lupsor-Platon 2015 [605]**
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=201)
Countries and Settings	Single centre, Romania
Funding	Study funded as part by the Iuliu-Hatieganu University of Medicine and Pharmacy, Cluj-Napoca.
Duration of study	January 2012 to June 2014

Study	Lupsor-Platon 2015 [605]
Age, gender, ethnicity	Mean age (SD): 49.10 (10.98); Sex 61.2% female; Ethnicity: NR
Patient characteristics	Consecutive patients with different diffuse chronic liver diseases (viral hepatitis C, viral hepatitis B, non-alcoholic steatohepatitis, primary biliary cirrhosis, autoimmune hepatitis). Exclusion criteria: the evidence of ascites at physical or ultrasound examination, other conditions associated with severe cholestatis or right heart failure, proven to influence the LS value, pregnancy, malignancy or other terminal disease, and a biopsy unsuitable for steatosis grading (when the biopsy contained <6 portal tracts). Liver disease aetiology: 58.7% HCV hepatitis, 23.88% HBV hepatitis, 23.88% NASH, and 5.47% other diffuse chronic liver disease (primary biliary cirrhosis, autoimmune hepatitis).
Index test	CAP with 3.5 MHz using Fibroscan. All performed by an experienced operator with long-term experience in the transient elastography measurements. During acquisition, patients were positioned in a dorsal decubitus positions, with the right arm in maxiumu abduction. Under TM and A-zone control, the operator chose a liver zone within the right lobe, free from any large vascular structure or the gallbladder. The final CAP value considered for analyisis was the median of 10 individual CAP values, regardless of the success rate. CAP was computed in an area located between 25 and 65mm from the skin and in the same region the biopsy specimen was taken from in order to grade and stage disease. Optimal CAP cut-off defined by maximisinh the sum of sensitivity and specificity: 285
Reference standard	Liver biopsy performed using the TruCut technique with a 1.8mm diameter automatic needle device. The specimens were fixed in formalin and embedded in paraffin. Only biopsy specimens with more than 6 portal tracts were eligible for evaluation. NASH was evaluated according to the Brunt system: by visual assessment of a percentage of hepatocytes with fatty accumulation. S0 steatosis <10% of hepatocytes, S1: 11-33%, S2: 34-66%, S3: 67-100%. The histological type of steatosis was specified as macrovesicular, microvesicular or mixed.
Target condition	Steatosis ≥ 34%

Study	Lupsor-Platon 2015 [605]
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 23 FP 25 FN 10 TN 143 Sensitivity 69% Specificity 85% PPV 48% NPV 93% Area under the curve 0.822 (0.76-0.87) General limitations according to QUADAS II: Index test threshold not pre-defined, unclear if index test interpreted without knowledge of reference standard.	

Study	Marsman 2011[634]
Study type	Retrospective analysis of records
Number of studies (number of participants	1 (n=36)
Countries and Settings	The Netherlands
Funding	None reported.
Duration of study	2003 to 2008
Age, gender, ethnicity	Mean age (SD) 59.6 years (9.0). Male 58%. Ethnicity NR
Patient characteristics	Patients who received neoadjuvant chemotherapy for colorectal liver metastases prior to liver resection. Patients were included when oxaliplatin-based CTx therapy was administered, an MRI with in-phase/opposed-phase (IP/OP) T1-weighted sequence, or a CT-scan including unenhanced phase was performed, and sufficient non-tumour bearing liver

Study	Marsman 2011[634]
	tissue was available in the resected liver specimen for histopathological analysis. 36/139 patients who underwent a liver resection following neoadjuvant CTx treatment had complete IP/OP MRI scans (MRI was not introduced as the modality of choice until towards the end of study timeframe). Mean BMI (SD): 26 kg/m^2 (4.0)
Index test	MRI Slides were evaluated by two independent pathologists blinded to the radiological measurements, for degree of steatosis. A 1.5 T MRI unit using identical scan protocols with a four-channel body array coil was used. Hepatic far content measurements were performed on T1 weighted in an opposed phase GRE sequences. Calculation of hepatic fat content was performed by measuring signal intensity (SI) values in IP/OP MR images using a picture archiving and analysis system (Impax). For measurements, ROI's were placed in the liver at paired anatomical position on IP/OP MR images avoiding major vessels, bile ducts and tumorous lesions. The mean liver SI in IP/OP images was calculated from a total of 12 ROI's placed in four different hepatic regions on three different transversal planes. The amount of hepatic fat (%RSID) was calculated using the formula ([SIin –SIout]/SIin) x 100% where SIin is the mean in-phase SI in the liver divided by the mean in-phase SI in the spleen, and SIout is represented by the mean opposed-[hawse SI in the liver divided by the mean opposed-phase SI in the spleen. A relative SI decrease (%RSID) in the liver OP images reflects the presence of an increased hepatic fat content. RSID values corresponding to histological cut-off values: -0.74% and 19.22%
Reference standard	Haematoxylin and eosin stained slides containing sufficient non-tumorous liver tissue were selected by two independent pathologists for histological evaluation. Radiologic follow-up was performed no more than 4 months preoperatively. Macrovesicular steatosis, present as lipid vacuole larger than the diameter of the nucleus, was graded as follows (Kleiner): S0 ≤5%, S1 5-33%, S2 34-66%, and S3 ≥66%
Target condition	Steatosis >5% Steatosis >33%

Study	Marsman 2011[634]	
Results: 2x2 table calculated using author-reported raw data TP 20 FP 4 FN 3 TN 9 Sensitivity 87% Specificity 69% PPV 83% NPV 75% Area under the curve NR		Results: 2x2 table calculated using author-reported raw data TP 7 FP 0 FN 2 TN 27 Sensitivity 78% Specificity 100% PPV 100% NPV 93% Area under the curve NR
General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection		

Study	Masaki 2013[638]
Study type	Prospective study
Number of studies (number of participants	1 (n=155)
Countries and Settings	Japan
Funding	None reported
Duration of study	April to December 2012
Age, gender, ethnicity	Median age (range): 55 years (24-91). Male 59%. Ethnicity NR
Patient characteristics	Patients with suspected chronic hepatitis due to any aetiology. Median BMI (range): 24.4 kg/m^2 (15.4-39.2) Liver disease aetiology: Hepatitis B 11%, Hepatitis C 37%, NASH 26%, other 26%

Study	Masaki 2013[638]
Index test	CAP CAP subject to same criteria as liver stiffness measurement using VCTE system which generates a 50=Hz shear wave that is longitudinally polarized along the ultrasound axis. CAP designed to measure liver ultrasonic attenuation (along the go and return path) at 3.5 MHz using the signals acquired by the FibroScan M probe. The LSM and CAP were obtained simultaneously and in the same volume of liver parenchyma (at depths between 25-65 mm). The median of the individual CAP values was used as the final CAP value. Optimal cut-off 232.5 dB/m
Reference standard	Liver biopsy on the same day as CAP using a 1.2mm/1.6mm diameter Menghini needle. Liver specimens >20mm in length were fixed, embedded in paraffin, and stained with haematoxylin and Masson trichome. One experienced pathologist analysed all the biopsies without knowledge of clinical data. Steatosis was graded according to Kleiner method: S0 ≤5%, S1 5-33%, S2 34-66%, and S3 ≥66%
Target condition	Steatosis ≥5%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 47 FP 23 FN 7 TN 78 Sensitivity 87% Specificity 77% PPV author-reported 75%, calculated using study prevalence 76% NPV author-reported 87%, calculated using study prevalence 92% Area under the curve 0.878 (0.818-0.939) General limitations according to QUADAS II: Index test threshold not pre-defined and unclear if interpreted without knowledge of the reference standard.	

Study	Mathiesen 2002[641]
Study type	Prospective study
Number of studies (number of participants	1 (n=165)
Countries and Settings	Two centres, one university hospital one county hospital, Sweden
Funding	NONE REPORTED
Duration of study	Feb 1988 to Feb 1991
Age, gender, ethnicity	Mean male age (range): 45.7 years (22-75). Mean female age (range): 53.8 years (23-77) .Male 67%. Ethnicity NR
Patient characteristics	Patients with no signs or symptoms of liver disease referred because of slightly to moderately raised ALT or AST (0.7-5 µkat/l) for more than six months. Liver disease aetiology: Heapatitis C 15%, alcoholic liver disease 8.5%, autoimmune hepatitis 2%, NAFLD 2%, A1 antitrypsin deficiency 1 %, primary biliary cirrhosis 1%, fatty liver 40%, fibrosis 5%, cirrhosis 1%, chronic mild hepatitis 14.5%, chronic sever hepatitis 9%, transaminitis 3% Mean BMI males (SD) 27.4 kg/m^2 (4.0), mean BMI females (range) 27.4 kg/m^2 (4.6)
Index test	Ultrasound performed by two experienced radiologists using Acuson XP 128 high resolution, real time sectional scanners with 2.5-2.35 MHz-transducers. Radiologists were unaware of clinical details. Liver assessed for size, contour, echogenicity, structure, penetration of ultrasound bean (posterior attenuation) and portal vessel wall distinction. Echogenicity scored on five=point scale (relative to the right kidney) 0: slightly reduced, 1 normal, 2 slightly increased, 3 clearly increased and 4 markedly increased. Patients were grouped into normal echogenicity (0-1) and raised echogenicity (2-4). Structure was judged as either homogenous or course echo pattern. The beam penetration was scored on a four-point scale: 1 normal, 2 slightly reduced, 3 clearly reduced, and 4 markedly reduced. Portal vessel wall distinction was scored on a four-point scale: 1 normal, 2 slightly reduced, 3 clearly reduced, and 4 markedly reduced. US was carried out within one week of biopsy in 120 patients, within two weeks in 20 patients, and within four week in 10 patients. The remaining 13 had a longer time interval between ultrasound and biopsy.
Reference standard	Percutaneous liver biopsy performed in all patients with a modified Menghini technique using a Hepafix 1.4 or 1.6mm needle. Biopsy specimens examined by the same pathologist without knowledge of the clinical, laboratory or ultrasound data, on two occasions 3-30 months apart. The degree of steatosis was scored as: 0 no fatty infiltration, 1 mild (<1.3 of area occupied by vacuoles), 2 moderate (1/3-2/3 of area occupied by vacuoles) and 3 pronounced fatty infiltration (more than 2/3 occupied by vacuoles). For comparison with ultrasound score 0-1 was meant to indicate no

Study	Mathiesen 2002[641]
	significant steatosis, while scores of 2 and 3 indicated presence of steatosis.
Target condition	Steatosis <33%
Results: 2x2 table calculated using author-reported raw data TP 85 FP 13 FN 9 TN 58 Sensitivity 90% Specificity 87% PPV 87% NPV 87% Area under the curve NR General limitations according to QUADAS II: Unclear patient selection procedures (consecutive or random, unclear exclusion criteria).	

Study	Mennesson 2009[655]
Study type	Prospective study
Number of studies (number of participants	1 (n=40)
Countries and Settings	Single institution, France
Funding	None reported
Duration of study	April 2007 to Feb 2008
Age, gender, ethnicity	Mean age (range): 52.5 years (23-78). Male 50%. Ethnicity NR
Patient characteristics	Asymptomatic patients with an incidentally discovered elevation in liver enzymes, no history of excessive alcohol

Study	Mennesson 2009[655]
	intake, negative results of viral screening, and no liver mass on ultrasound referred for biopsy for diagnostic purposes. Liver disease aetiology: NAFLD 62.5%, alcoholic 25%, cholangiopathy 5% and autoimmune hepatitis 7.5%
Index test	T1-weighted MRI in- and opposed-phase images. One radiologist blinded to clinical and pathological results recorded signal intensity (SI) by mean regions of interest placed at the same location in both phases. Fat-water ratio was obtained by dividing SI of liver opposed-phase sequence by SI of liver in in-phase sequence. Cut-off value fat-water ratio >0
Reference standard	Ultrasound-guided liver biopsy performed same d as MRI using a 14-gauge needle in variable segments in the right hepatic lobe. Samples were fixed in buffered formalin and embedded in paraffin. Sections 4µm thick were stained in haematoxylin-eosin-saffron, Perls iron stain and chromotope and evaluated by one pathologist blind to clinical information. Liver steatosis was reported aas a quantitative evaluation of the percentage of hepatocytes containing macrovesicularor microvesicular fat. Grade 0: <5%, grade I: 6-33%, grade II: 34-66%, and grade III >66%.
Target condition	Steatosis >5%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 32 FP 1 FN 1 TN 6 Sensitivity 97% Specificity 86% PPV NR NPV NR Area under the curve NR General limitations according to QUADAS II: Unclear if index test threshold was pre-defined	

Study	Myers 2012[679]
Study type	Prospective study
Number of studies (number of participants	1 (n=153)
Countries and Settings	Multicentre trial, five hepatology centres, Canada
Funding	Study supported by Echosens.
Duration of study	July 2009 to July 2010
Age, gender, ethnicity	Median age (IQR): 50 years (41-56). Male 69%.
Patient characteristics	Adults (≥ 18 years) with chronic liver disease and BMI ≥ 28 kg/m^2 Exclusion criteria: contraindications to liver stiffness measurement (e.g. pregnancy), BMI <28 kg/m^2, previous liver transplant, malignancy or other terminal disease, and refusal to undergo biopsy. Liver disease aetiology: NAFLD 47%, chronic viral hepatitis 44%, other 9%
Index test	CAP Ultrasonic attenuation measured at 3.5 MHz using signals acquired by the FibroScan M probe based on vibration-controlled transient elastography. CAP obtained simultaneously and in the same volume of liver parenchyma as liver stiffness measurement. Final CAP value is the median of individual measurements. Optimal thresholds defined by maximal sum of sensitivity and specificity: 289 and 288 dB/m
Reference standard	Liver biopsies were fixed, paraffin-embedded and stained with at least haematoxylin and eosin and Masson's trichome. Two experienced hepatopathologists analysed biopsies independently without knowledge of clinical data. Steatosis graded according to the NAFLD activity score (NAS): S0 <5%, S1 5-33%, S2 34-66%, and S3 >66%
Target condition	Steatosis ≥5% Steatosis >33%

Study	Myers 2012[679]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥5%** TP 77 FP 5 FN 36 TN 35 Sensitivity 68% Specificity 88% PPV 94% NPV 49% Area under the curve 0.79 (0.71-0.87)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis >33%** TP 46 FP 38 FN 8 TN 61 Sensitivity 85% Specificity 62% PPV 55% NPV 88% Area under the curve 0.76 (0.69-0.84)
General limitations according to QUADAS II: Unclear interval between CAP and liver biopsies (suggests would be up to six months), unclear if CAP interpreted without knowledge of biopsy diagnosis and index test threshold not predefined.		

Study	Palmentieri 2006[736]
Study type	Prospective study
Number of studies (number of participants	1 (n=235)
Countries and Settings	Italy
Funding	None reported
Duration of study	Jan 2001 to Dec 2003
Age, gender, ethnicity	Median age (range): 52 years (17-72). Male 53%. Ethnicity NR

Study	Palmentieri 2006[736]
Patient characteristics	Suspicion of liver disease of various aetiologies. Liver disease aetiologies: NAFLD 14%, hepatitis B 13%, hepatitis C 62%, both hepatitis B and C 1%, non-Hodgkin's lymphoma 7%, other 3%
Index test	Real-time ultrasound scanning performed by two internal medicine specialists. Ultrasound examination was used to determine various liver echo patterns with a convex probe at the frequency of 3.7 MHz: homogenous liver pattern, bright liver echo pattern, and coarse liver echo pattern. Bright liver signified a discrepancy higher than expected in the echo amplitude between liver and kidney parenchyma, was considered the pattern indicating steatosis. The degree of steatosis was determined by the fall in echo amplitude (i.e. rate of posterior bean attenuation due to high reflectivity of the steatotic parenchyma) which demonstrated a reduction in intensity depth (type 1), a loss of echoes from the diaphragm (type 2) or a loss of echoes from the walls of the portal vein (type 3).
Reference standard	Echo-assisted biopsy from the right hepatic lobe using a 17-gauge Menghini modified needle inserted through the intercostal space. Specimens were fixed in formalin, embedded in paraffin and evaluated by Masson's trichome staining. Degree of steatosis based on the number of fat-replete hepatic cells per microscopic field categorised as: 0-2%, 3-49%, >50%.
Target condition	Steatosis ≥30%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 64 FP 5 FN 7 TN 140 Sensitivity 90% Specificity 97% PPV 96% NPV 92% Area under the curve NR General limitations according to QUADAS II: Unclear interval between index test and reference standard and unclear if index test interpreted without knowledge of reference standard results.	

Study	Paparo 2015 [739]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=77)
Countries and Settings	Single centre unit of infectious diseases, Italy
Funding	Supported by a grant from Fondazione Carige
Duration of study	1 January 2013 to 31 December 2013
Age, gender, ethnicity	Mean age (SD): 51.31 (11.27); Sex 55.8% male; Ethnicity: NR
Patient characteristics	Consecutive untreated (not under inferno-based therapies) people with chronic viral hepatitis C. Exclusion criteria: contraindications to 1.5T MRI (cardiac pacemaker, claustrophobia, foreign bodies and implanted medical devices with ferromagnetic properties) and/or to liver biopsy (uncorrectable coagulopathy).
Index test	MRI and proton density fat fraction (PDFF) – MRI of the liver performed in supine position on a 1.5T MRI scanner using a phased array, eight-element, and flexible torso coil. A 2D spoiled and multi-echo gradient-echo sequence with 16 echoes was performed in the axial plane to measure hepatic PDFF. The parameters of this sequence were adjusted in order to achieve a complete correction for confounding factors such as T1 bias, T2* decay, and water-fat signal interference. To minimise T1 effects, a 20° flip angle was used at repetition time (TR) ranging from 120 to 270 msec, adjusted by the technologist to individual breath-hold capacity. To estimate water-fat signal interference and T2* effects, 16 echoes were obtained at serial opposed-phase and in-phase echo times during a single breath hold of 12-34 seconds. Other imaging parameters were 10mm section thickness, 0 intersection gap, 125 kHz bandwidth, one signal average, and rectangular field of view with a 128 x 96 matric adjusted to individual body habitus and breath-hold capacity. Cut off determined to maximise the sum of sensitivity and specificity. For steatosis 5% optimal cut-off = 6.87, for steatosis 33% optimal cut-off = 11.08
Reference standard	Ultrasound-assisted percutaneous liver biopsy was performed with an intercostal approach using 15 to 18-gauge needles. All biopsy specimens were fixed in formalin and embedded in paraffin. A single expert liver pathologist, blind to the results of the index tests, read the specimens on site. Liver steatosis was determined estimating the percentage of fat-containing hepatocytes on hematoxylin-eosin stained specimens and graded according to the Kleiner method. S0 steatosis in fewer than 5% of hepatocytes; S1 5-33%; S2 34-66% and S3 more than 66%.

Study	**Paparo 2015** [739]	
Target condition	Steatosis ≥5% Steatosis ≥ 34%	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥5%** TP 27 FP 1 FN 4 TN 45 Sensitivity 87.1% Specificity 97.83% PPV 96.4% NPV 91.8% Area under the curve 0.926 (0.843-0.973)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥34%** TP 7 FP 8 FN 1 TN 61 Sensitivity 87.5% Specificity 88.1% PPV 46.7% NPV 98.4% Area under the curve 0.929 (0.847-0.975)
General limitations according to QUADAS II: All patients underwent MRI, transient elastography and liver biopsy within a time interval of <10 days. Blinding for reference standard and index test results. Thresholds not pre-defined.		

Study	**Perez 2007**[758]
Study type	Retrospective analysis of medical records
Number of studies (number of participants	1 (n=131)
Countries and Settings	Single centre university hospital, USA
Funding	None reported
Duration of study	From January 2003 to July 2004

Study	Perez 2007[758]
Age, gender, ethnicity	Mean age (SD) only reported by outcome: Normal 51.2 years (7.8); Fatty liver 52.4 years (8.6); non-specific 52.7 years (9.5). Male 56.5%. African American 86%
Patient characteristics	Indications for liver biopsy: chronic hepatitis C 89%, chronic hepatitis B 4%, persistently abnormal liver tests 5%.
Index test	Ultrasound as interpreted by initial radiologist (not reanalysed by research team) – individual judgement in reporting 'increased echogenicity' and 'fatty liver'. If the final impression mentioned fat, steatosis, fatty metamorphosis or fatty liver it was considered consistent with fatty liver. A secondary interpretation on the body of the US report focussing on echogenicity grouped results into three categories – normal, increased echogenicity and heterogeneous. If the report mentioned homogenous increased echogenicity, increased echogenicity, bright liver, or increased attenuation then it was considered increased echogenicity.
Reference standard	Liver biopsies performed using a standard needle-core device for evaluation of liver disease. 63% were ultrasound-guided, 37% were obtained using percussion and palpation for needle positioning. Fat was graded as grade 0: no fat, grade 1: ≤33% fat, grade 2: 33-66%, and grade 3: ≥66% Ultrasound was performed within 3 months of biopsy in 81% of patients, and within 9 months for remaining patients.
Target condition	Steatosis >33%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 2 FP 16 FN 15 TN 98 Sensitivity 11% Specificity 86% PPV NR NPV NR Area under the curve NR General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection. Unclear whether ultrasounds interpreted without knowledge of reference standard and widely varying interpretations and thresholds. Population received slightly different reference standards, and different range of intervals between ultrasound and reference standard.	

Study	Sasso 2010[841]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=115)
Countries and Settings	Five liver units, France
Funding	None reported
Duration of study	Not reported
Age, gender, ethnicity	Mean age (SD) 49 years (12). Male 64%. Ethnicity NR
Patient characteristics	Reffered for liver biopsy regardless of the cause of liver disease. Liver disease aetiology: Chronic hepatitis C 36%, chronic hepatitis B 15%, alcoholic liver disease 34%, NAFLD 15%
Index test	CAP by FibroScan using the regular 3.5 MHz probe and regular acquisition procedure. Final CAP results corresponded to the median of all individual CAOP measured on each valid liver stiffness measurement. CAP examination was also performed in the right lobe of the liver in the intercostal space. Cut-off maximising total sensitivity and specificity 259.4 dB/m
Reference standard	Liver biopsies were all performed on the right lobe of the liver between the rib bones. Steatosis was appraised as a percentage or range of percentage of hepacytes with fatty accumulation. Steatosis was pooled by the following grading system S0: 0-10%, S1: 11-33%, S2: 34-66%, S3: 66-100%. Liver biopsy and FibroScan performed within 7 days
Target condition	Steatosis ≥34%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 32 FP 11 FN 4 TN 68 Sensitivity 89% Specificity86% PPV 80%	

Study	Sasso 2010[841]
NPV 92% Area under the curve 0.95 (0.91-1.00) General limitations according to QUADAS II: Unclear if index test interpreted without knowledge of reference standard results and index test threshold not predefined.	

Study	Sasso 2012[839]
Study type	Prospective study
Number of studies (number of participants	1 (n=615)
Countries and Settings	Multicentre, five hospital liver units, France
Funding	First author and three others work for Echosens
Duration of study	Between November 2002 and December 2004
Age, gender, ethnicity	Mean age (SD) 47.9 years (11.6). Male 64%. Ethnicity NR
Patient characteristics	Presence of active hepatitis C infection and histological pattern of chronic hepatitis. Mean BMI (SD): 24.1 kg/m^2 (3.7)
Index test	CAP designed to measure liver ultrasound attenuation at 3.5 MHz using signals acquired by FibroScan. CAP was measured only on validated measurements according to the same criteria as liver stiffness and on the same signals. Ensures the operator obtains a liver ultrasonic attenuation simultaneously and in the same volume of liver parenchyma as the liver stiffness measurement (between 25-65 mm). The final CAP was the median of individual CAP values. Optimal cut-off to maximise total sensitivity and specificity: 233 dB/m
Reference standard	Liver biopsies specimens were fixed in formalin and embedded in paraffin. Sections 4µ thick were stained with haematoxylin-eosin-safran and picro0sirius red. All specimens were analysed by the sane hepapathologist blinded to CAP results. Steatosis was categorised by visual assessment as S0: <10% hepatocytes, S1: 11-33% hepatocytes, S2: 34-66% hepatocytes, and S3: 67-100% hepatocytes. All CAP performed within 90 days of liver biopsy.

Study	Sasso 2012[839]
Target condition	Steatosis ≥34%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 69 FP 139 FN 10 TN 397 Sensitivity 87% Specificity 74% PPV 33% NPV 98% Area under the curve 0.86 (0.81-0.92) General limitations according to QUADAS II: Unclear if index test interpreted without knowledge of reference standard results and index test threshold not predefined.	

Study	Schwimmer 2015 [851]
Study type	Prospective study
Number of studies (number of participants)	1 (n=174)
Countries and Settings	Single university medical centre, USA
Funding	None reported
Duration of study	Unclear
Age, gender, ethnicity	Mean age (SD) years: No steatosis 15.1 (2.5); 5-33% steatosis 14.2 (2.2); 34-66% steatosis 14.1 (2.2); >67% steatosis 13.2 (2.0).Percentage male: No steatosis 54%; 5-33% steatosis 70%; 34-66% steatosis 68%; >67% steatosis 72%. Ethnicity NR
Patient characteristics	Children aged 8-17 years who had already undergone liver biopsy as part of a clinical evaluation for liver disease.

Study	Schwimmer 2015 [851]
Index test	MRI proton density fat fraction (PDFF) Children were scanned at 3T using an advanced magnitude-based liver far quantification MRI technique. This gradient-recalled-echo technique estimates liver PDFF using a low flip angle and a repetition time of ≥150 milliseconds to minimise T1 bias and six gradient-recalled echoes to calculate and correct T2* signal decay. PDFF values were obtained by placing regions of interest (ROI) in representative portions of the liver. PDFF values in ROIs placed in each of the four right-lobe segments were averaged to provide a composite right-lobe MRI-estimated PDFF value. The MR technologist and image analyst were unaware of steatosis grade results.
Reference standard	Liver biopsy determination done clinically and was not part of the current study. Hepatopathologists were not aware of MRI results. Diagnosis of NAFLD based on exclusion of other causes of steatosis by clinical history, laboratory studies and histological demonstration of ≥5% of hepatocytes containing macrovesicular fat.
Target condition	Steatosis ≥ 5%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 102 FP 1 FN 48 TN 23 Sensitivity 68% Specificity 96% PPV 84% NPV 43% Area under the curve 0.82 General limitations according to QUADAS II: Unclear exclusions and recruitment of children, case-control not avoided, index test threshold based on previously published cut off, unclear timing between index test and reference standard (as reference standard performed previously outside of the study.	

Study	Shen 2014[867]
Study type	Prospective study
Number of studies (number of participants	1 (n=152)
Countries and Settings	Multicentre, three liver centres, China
Funding	Supported by the National Key Basic Research Project; Chinese Foundation for Hepatitis Prevention and Control – 'Wang Bao-En' Liver Fibrosis Research Fund; Shanghai Science and Technology Committee; and the 100-Talents Programme of the Shanghai Municipal Health Bureau.
Duration of study	Between March 2012 and March 2013
Age, gender, ethnicity	Mean age (range) 35 years (28-49). Male 69%. Ethnicity NR.
Patient characteristics	Adults (≥18 years) Mean BMI (range): 24.9 kg/m^2 (22.5-27.7) Exclusion criteria: alcohol intake, other disease that lead to fatty liver (chronic hepatitis C, drug-induced liver disease, total parenteral nutrition, hepatolenticular degeneration, autoimmune liver disease), previous liver transplantation, other terminal disease or malignancy, contraindications for FibroScan or unreliable CAP measurements, refusal to undergo biopsy or disqualified liver specimens. Liver disease aetiology: NAFLD 34%, chronic hepatitis B 66%
Index test	CAP performed by one certified operator blinded to liver histology. FibroScan 502 equipped with M probe using the same reliability of liver stiffness measurements. Optimal cut-offs by maximising the sum of sensitivity and specificity (maximum Youden index): 253 dB/m and 285 dB/m
Reference standard	Percutaneous liver biopsy performed with an 18-gauge BARD Max-Core Disposable Biopsy Instrument from the right lobe under real time ultrasound guidance. Specimens were formalin-fixed, paraffin-embedded, sectioned and stained with HE, Masson's trichome and reticulin. The presence of ≥5% of hepatocytres was considered to represent fatty liver which was evaluated by light microscopic examination of an HE liver section (4-5µm thick) under a 10x objective lense. Steatosis was categorised as S0: <5%, S1: 5-33%, S2: 34-66%, S3 ≥67% according to NAS. Biopsy and CAP within 4 weeks.
Target condition	Steatosis ≥5% Steatosis ≥34%

Study	Shen 2014[867]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥5%** TP 79 FP 11 FN 10 TN 52 Sensitivity 89% Specificity 82.5% PPV 89% NPV 84% Area under the curve 0.92 (0.88-0.97)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥34%** TP 42 FP 18 FN 3 TN 89 Sensitivity 93% Specificity 83% PPV 70% NPV 97% Area under the curve 0.92 (0.87-0.97)
General limitations according to QUADAS II: Index test threshold not pre-specified.		

Study	Tang 2015 [941]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=89)
Countries and Settings	Single centre, USA
Funding	One author received grants from NDDK and General Electric Healthcare. One author reports contracted work for Bayer, Genzyme, Isis, Janssen, Pfizer, Sanofi, Synageva and Takeda.
Duration of study	December 2009 to July 2013
Age, gender, ethnicity	Mean age (range): 51 (22-80); Sex 43% male; Ethnicity: NR

Study	Tang 2015 [941]	
Patient characteristics	Adults (≥18 years) known to have or suspected of having NAFLD in whom other causes of liver disease were excluded clinically, who underwent research MR examinations and standard-of-care clinical liver biopsy within a 180 days. Exclusion criteria: regular and excessive alcohol consumption within 2 years prior to recruitment, with ≥14 drinks for men or ≥7 drinks for women per week; use of steatogenic or hepatoxic drugs; clinical or laboratory evidence of secondary NAFLD due to major nutritional and iatrogenic gastrointestinal disorders or to human immunodeficiency virus infection; clinical or laboratory evidence of liver disease other than NAFLD such as viral hepatitis, Wilson disease, hemochromatosis, glycogen storage disease, alpha-antitrypsin deficiency, autoimmune hepatitis, cholestatic liver disease, and vascular liver disease; contraindication(s) to MR imaging; pregnancy or trying to become pregnant.	
Index test	MR imaging in supine position with a standard torso phased-array coil centred over the liver at 3.0 T with an eight-channel receive coil. To estimate MR imaging proton density fat fraction (PDFF), unenhanced axial images were obtained using a low-flip-angle, six-echo, two-dimensional spoiled gradient-recalled-echo sequence, MR imaging PDFF maps generated using an algorithm that estimates T2* and PDFF by taking into account multi-frequency interference of protons in fat. Trained analysts blinded to histological data reviewed MR images. The PDFF in each of the nine regions of interest were recorded and the PDFF value across the entire liver was reported as the mean of the PDFF values of all nine ROIs. Additionally the R2* value (calculated as 1/T2*) in each of the nine ROIs was recorded and the mean R2* value across nine ROIs was calculated. Thresholds based on NASH CRN ancillary study-derived MR imaging PDFF thresholds: 6.4% for S0 vs. ≥S1; 17.4% for ≤S1 vs. ≥S2; 22.1% for ≤S2 vs. ≥S3	
Reference standard	Non-targeted percutaneous liver biopsy of the right liver lobe using an intercostal approach in a peripheral location with a 16- or 18-gauge needle. A hepatopathologist blinded to radiological data scored steatosis according to the proportion of hepatocytes with macrovesicular steatosis and converted to a four-point score as defined by the NASH CRN scoring system: S0 <5%, S1 5-33%, S2 33-66% and S3 >66%.	
Target condition	Steatosis ≥5% Steatosis ≥ 33%	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥5%** TP 71 FP 1		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥33%** TP 28 FP 2

Study	Tang 2015 [941]	
	FN 12 TN 5 Sensitivity 86% Specificity 83% PPV 99% NPV 29% Area under the curve 0.961 (0.905-1.00)	FN 16 TN 43 Sensitivity 64% Specificity 96% PPV 93% NPV 73% Area under the curve 0.947 (0.908-0.987)
General limitations according to QUADAS II: Index test threshold pre-defined, clearly described blinding of both radiologist and histopathologist. Timing between MR and biopsy ranged from 0 to 173 days (median 35 days). Unclear if recruitment was consecutive.		

Study	Urdzik 2012[984]
Study type	Prospective study
Number of studies (number of participants	1 (n=35)
Countries and Settings	Single centre university hospital, Sweden
Funding	ALF-grants from the Departments of Surgery and Diagnostic Radiology
Duration of study	January 2007 to December 2009
Age, gender, ethnicity	Mean age (SD): 62.6 years (9.4). Male 71%. Ethnicity NR
Patient characteristics	Patients with colorectal liver metastasis. Planned resection of minimum two liver segments allowing sufficient non-tumourous liver tissue for histology.
Index test	^{1}H-MRS performed the day before liver resection. Single voxel H-spectra measured by 3T scanner Achieva using STEAM sequence in free-breathing (TR/TM/TE 3000/18/15ms, spectral bandwidth 2000Hz, 1024 points, 16 phase cycles steps). Magnetic field homogeneity was improved by iterative first-order shimming. 16 non-water suppressed and 32-water suppressed scans. Volume of interest 30x30x30mm^{3}was placed on non-tumorous liver parenchyma. Water and fat (methylene) spectral intensitities

Study	Urdzik 2012[984]
	were corrected for T1 and T2 relaxation using T1=809ms, T2=34ms for water and T1=383ms and T2=68ms for fat. The percentage of liver fat (intracellular-triglyceride content) was computer as methylene/(water + methylene) spectral intensity ratio x 100. Best threshold 10.2%
Reference standard	Non-tumourous parenchyma samples obtained directly after surgery by taking tissue blocks approximately 40x40x7mm. Samples were fixed directly in 10% neutral buffered formalin (4% formaldehyde), embedded in paraffin blocks, cut into 3µm thickness and stained with haematoxylin and eosin and can Gieson. All samples evaluated by one experienced pathologist blinded to MRS results. Steatosis was graded as described by Kleiner: ≤5%, 5-33%, 33-66%, ≥66%
Target condition	Steatosis ≥33%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 9 FP 2 FN 0 TN 24 Sensitivity 100% Specificity 92% PPV 82% NPV 100% Area under the curve 0.983 (0.951-1.00) General limitations according to QUADAS II: Unclear how index test threshold defined.	

Study	van Werven 2010[994]
Study type	Prospective study
Number of studies (number of participants	1 (n=46)

Study	van Werven 2010[994]
Countries and Settings	The Netherlands
Funding	None to disclose
Duration of study	November 2007 through March 2009
Age, gender, ethnicity	Mean age (range): 58.7 years (27-76). Male 54%. Ethnicity NR
Patient characteristics	Adults (≥18 years) scheduled for liver resection. Indications for liver resection: colorectal metastases 49%, adenoma 15%, cholangiocarcinoma 13%, focal nodular hyperplasia 4%, hepatocellular carcinoma 2%, haemagioma 2%, gallbladder carcinoma 2%, mamma carcinoma metastasis 2%, metastasis of neuroendocrine tumour 2%, choledochal cyst 2%, stenosis ductus hepaticus 2%, intrahepatic bile duct stones 2% Exclusions: pregnancy, acute liver resection and MR contraindications
Index test	MRI, MRS, ultrasound T1-weighted dual-echo MR imaging using a 3.0 T Intera MR imager with a six-channel torso coil used to obtain MRI and MRS imaging during the same procedure. Opposed-phase and in-phase breath hold at three different sections with four regions of interest evenly distributed in the liver parenchyma. The mean signal intensity values of all ROI;s were determined at the same locations for in-phase and opposed-phase images. Mean fat fraction was calculated using SI-in – SI-opposed / 2SI-in where SI-in and SI-opposed are the meal liver signal intensity of all ROI's on in-phase and opposed-phase images respectively. MR physicist was blinded to study results. ^{1}H-MRS 20 x 20 x 20mm voxel positioned over the right lobe. Spectra were acquired using the first order iterative shimming and a point-resolved spectroscopy sequence. The water and fat resonance peaks located at 4.65 and 1.3ppm were fitted using a spectroscopic analysis package and relative fat content was expressed as a ratio of the fat peak atreas (1.3ppm/[1.3ppm + 4.65ppm]). Calculated peak areas of the water and fat were corrected for T2 relaxation (T2water = 34 msec, T2fat =68mse) and the percentage hepatic fat content was calculated according to Szezepaniak. Ultrasound performed with an iU22 device using a 2-5MHz probe or Elegra device using a 3-5MHz probe, An experienced abdominal radiologist blinded to other study results scored the degree of steatosis. On the basis of increasing echogenicity of the liver parenchyma compared to that of the right kidney and decreased visualisation of the diaphragm and intrahepatic vessel borders, steatosis in each patient was graded as none (normal US structure), mils (slight increase in echogenicity, normal visualisation), moderate (diffuse increase of echogenicity, slight impaired visualisation) or severe (marked increase of echogenicity, poor or no visualisation). All index tests performed within 2 weeks of liver resection. Best cut-offs while balancing the best sensitivity with the lowest false-positive rate: hepatic fat fraction MRI 1.5%, MRS

Study	van Werven 2010[994]		
	1.8%, ultrasound (no cut-off, presence or not of steatosis).		
Reference standard	Large wedge biopsy samples fixed in 10% buffered formalin for 24 hours, and 4µm thick sections were stained with haematoxylin eosin. An experienced hepatopathologist blinded to study results evaluated the liver biopsy and graded percentage of macrovesicular steatosis as: none (0-5%), mild (5-33%), moderate (33-66%) and severe (>66%).		
Target condition	Steatosis ≥5%		
Results: 2x2 table calculated using author-reported raw data **MRI** TP 19 FP 2 FN 2 TN 20 Sensitivity 90% Specificity 91% PPV 90% NPV 91% Area under the curve 0.93(95% CI not reported)	Results: 2x2 table calculated using author-reported raw data **MRS** TP 21 FP 3 FN 2 TN 20 Sensitivity 91% Specificity 87% PPV 88% NPV 91% Area under the curve 0.97(95% CI not reported)	Results: 2x2 table calculated using author-reported raw data **Ultrasound** TP 13 FP 5 FN 7 TN 17 Sensitivity 65% Specificity 77% PPV 72% NPV 71% Area under the curve 0.77 (95% CI not reported)	
General limitations according to QUADAS II: Index test thresholds not pre-defined.			

Study	van Werven 2011[995]
Study type	Prospective study
Number of studies (number of participants	1 (n=38)
Countries and Settings	The Netherlands

Study	van Werven 2011[995]
Funding	Supported by Nuts Ohra Foundation
Duration of study	January to December 2008
Age, gender, ethnicity	Median age (range) 45.5 years (22-63). Male 17%. Ethnicity NR
Patient characteristics	Adults (18 years or older) scheduled to undergo laparoscopic Roux-en-Y gastric bypass surgery. Indication for surgery was BMI >40 or >35 with comorbidity. Median BMI (range): 47.7 $kg.m^2$ (40.0-63.9) Exclusion criteria: pregnancy, contraindications to MRI, other causes of chronic liver disease, and the presence of alcoholic fatty liver disease.
Index test	^{1}H-MRS within four weeks prior to surgery After T1-weighted coronal and axial localiser images were acquired, a 20x20x20 mm voxel was positioned in the right liver lobe. Spectra were acquired with pencil beam second-order shimming in a predefined volume in the liver, a point-resolved spectroscopic sequence (PRESS) with TR/TE of 35/2000 and 64 signal acquisitions. A research fellow blinded to study results under direct supervision of an experience MR physicist processed the data. Signal resonances from water and fat located at 4.65 and 1.3ppm were analysed. Prior knowledge was used for peak localisation by use of soft constraints. Signal resonance were fitted with lorantzian line shapes. Phase variation was allowed around manually selected optimum. Relative fat content was expressed as a ratio of peak fat area of the cumulative water and fat peak areas: 1.3ppm/ (1.3ppm +4.65ppm). No correction for T1 relaxation was performed because no T1 weighting was present at a TR of 2000ms. Calculated peak areas of water and fat were corrected for T2 relaxation. Best cut-offs while balancing the best sensitivity with the lowest false-positive rate: hepatic fat fraction 5.7%
Reference standard	Liver specimens fixed in 10% buffered formalin for 24 hours, dehydrated, and embedded in paraffin. Sections 4µm thick treated with H&E and periodic acid-Schiff stain with and without diastase. Sections were scored by an experienced hepatopathologist blind to study results. Percentage of macrovesicular steatosis graded according to Kleiner: none (0-5%), mild (5-33%), moderate (33-66%) and severe (>66%).
Target condition	Steatosis >5%
Results: 2x2 table calculated using author-reported raw data TP 17 FP 1	

Study	van Werven 2011[995]
FN 3 TN 15 Sensitivity 85% Specificity 94% PPV 94% NPV 89% Area under the curve 0.91 General limitations according to QUADAS II: Index test thresholds not pre-defined.	

Study	Wang 2013[1019]
Study type	Prospective study
Number of studies (number of participants	1 (n=175)
Countries and Settings	Single centre, Taiwan
Funding	None reported
Duration of study	Between Feb 2007 and March 2008
Age, gender, ethnicity	Mean age (SD): 45.6 years (11.7). Male 59%. Ethnicity NR
Patient characteristics	Consecutive patients with chronic hepatitis and indication for percutaneous liver biopsy. Excluded: patients with liver cyst, chronic renal failure or renal cyst that hinder ultrasound examination. Liver disease aetiology: Chronic hepatitis B 31%, chronic hepatitis C 60.5%, chronic hepatitis B with C infection 4.5%
Index test	Ultrasound with 3.75 MHz convex probe on the same day as biopsy. The probe was positioned in a right intercostal scan so that stable parenchyma images of the liver and right kidney were obtained simultaneously. The echo intensities of the liver and right renal parenchyma were measured. Each region of interest was chosen in hepatic parenchyma and right renal parenchyma at the same level where a homogenous 10cm depth from the liver surface was located. Hepatorenal contrast was assessed from the difference or ratio in echo-intensity between the mean value of hepatic parenchyma and that of right renal parenchyma. All

Study	Wang 2013[1019]	
	ultrasound examinations were performed without knowledge of biopsy results. The severity of fatty change was classified into mild (the presence of hyperechoic liver tissue with normal beam penetration and visualisation of diaphragm with portal vein borders), moderate (the moderate spread and increase of echo intensity with decreased beam penetration), and severe (the marked increase in intensity with no echoes visualisation of portal vein border, obscured diaphragm and posterior portion of the right lobe, and reduced visibility of kidney). Optimal cut-off value: the point with the shortest 'distance' defined as $\sqrt{[(1\text{-sensitivity})^2 + (1\text{-specificity})^2]}$:	
Reference standard	Liver biopsy from segment 5 or 6 using a 16-gauge true-cut needle under ultrasound guidance. Biopsy specimens stained with haematoxylin-eosin, and one pathologist blinded to ultrasound results assessed the extent of hepatic steatosis. Steatosis arbitrarily graded as <5%, 5-9%, 10-19%, 20-29% and ≥30% of hepatocytes with fat deposits.	
Target condition	Steatosis ≥5% Steatosis ≥30%	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥5%** TP 91 FP 24 FN 20 TN 40 Sensitivity 82% Specificity 62.5% PPV 79% NPV 67% Area under the curve 0.760 (0.688-0.833)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Steatosis ≥34%** TP 24 FP 22 FN 4 TN 125 Sensitivity 86% Specificity85% PPV 52% NPV 98% Area under the curve 0.927 (0.881-0.972)
General limitations according to QUADAS II: Index test thresholds not pre-defined.		

Study	Wang 2014[1014]
Study type	Retrospective chart review
Number of studies (number of participants	1 (n=171)
Countries and Settings	Single centre, Taiwan
Funding	Supported
Duration of study	Between 2007 and 2009
Age, gender, ethnicity	Mean age (SD) 54 years (13.2). Male 58%. Ethnicity NR
Patient characteristics	Patients with various causes of hepatitis Liver disease aetiology: chronic hepatitis B 36%, chronic hepatitis C 51%, hepatitis B and C co-infection 5%, NAFLD 6%, acute hepatitis C 1%, drug induced hepatitis 1%, autoimmune hepatitis 1%
Index test	Ultrasound medical records. Ultrasound obtained either with a 4 MHz electronic probe or a 5 MHz electronic probe. One of ten hepatologists interpreted results. If the echogenicity of the liver was the same as the renal cortex, defined as negative steatosis. A slight increase of lover echogenicity with clear vascular wall and diaphragm defined mild steatosis. In moderate steatosis, visualisation of vascular wall and diaphragm was impaired and blurred. Severe steatosis was recognised as marked increase brightness, far-field beam attenuation of the posterior segment of the right lobe of liver, and no visualisation of vascular wall and diaphragm.
Reference standard	Echo-guided percutaneous liver biopsy from the right hepatic lobe using an 18 gauge biopsy needle. Samples fixed with formalin, embedded with paraffin, and stained with haematoxylin and eosin. One experienced pathologist blinded to clinical data evaluated samples. Hepatic steatosis categorised as negative ≤5%, mild 6-33%, moderate 34-66% and severe ≥67%
Target condition	Steatosis >5% Steatosis ≥34%

Study	Wang 2014[1014]	
Results: 2x2 table calculated using author-reported raw data **Steatosis >5%** TP 43 FP 27 FN 17 TN 84 Sensitivity 72% Specificity 76% PPV 61% NPV 83% Area under the curve NR		Results: 2x2 table calculated using author-reported raw data **Steatosis ≥34%** TP 15 FP 13 FN 7 TN 136 Sensitivity 68% Specificity 91% PPV 54% NPV 95% Area under the curve NR
General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection. Unclear interval between index test and reference standard (median one month, range 0-10months).		

Study	Wang 2014[1018]
Study type	Prospective study
Number of studies (number of participants	1 (n=88)
Countries and Settings	Single centre, China
Funding	China Hepatitis Prevention and Treatment Foundation Wang Baoen Liver Fibrosis Research Fund
Duration of study	August to December 2012
Age, gender, ethnicity	Mean age (SD, range) 38.32 years (12.99, 15-67). Male 70%. Ethnicity NR
Patient characteristics	Patients with chronic hepatitis B
Index test	CAP Decision points positioned between the seventh and eighth ribs or between the eighth and ninth ribs from the right

Study	Wang 2014[1018]
	anterior axillary line to the midaxillary line. After 10 consecutive valid detections, median was selected as the ultimate measurement. The success rate of ultimate detection was required to exceed 60%, and in the interquartile range should be less than 1/3 of the median. Optimal cut-off selected according to ROC curve 230 dB/m
Reference standard	Liver biopsy fixed in 10% neutral formalin and embedded in paraffin. Hepatic steatosis was quantified as S0: liver far content/liver wet ratio ≤10%, S1 11-33%, S2: 34-66% and S3 67-100%
Target condition	Steatosis ≥34%
Results: 2x2 table calculated using author-reported sens, spec and study prevalence TP 20 FP 14 FN 4 TN 50 Sensitivity 83% Specificity 78% PPV 65% NPV 89% Area under the curve 0.868 (0.748-0.989) General limitations according to QUADAS II: Unclear patient selection and exclusion criteria, unclear flow and timing between index test and reference standard, and threshold not pre-specified.	

Study	Webb 2009[1027]
Study type	Retrospective analysis of medical files
Number of studies (number of participants	1 (n=111)
Countries and Settings	Single centre liver unit, Israel

Study	Webb 2009[1027]
Funding	None reported
Duration of study	April 2005 to March 2006
Age, gender, ethnicity	Mean age (SD) 44 years (12). Male 54%. Ethnicity NR
Patient characteristics	Indications for liver biopsy: hepatitis C infection 50%, hepatitis B virus 3%, NAFLD 39%, unexplained elevation of liver enzymes 8%. Restricted to patients with diffuse homogenous hyperechogenicity of the liver. Excluded patients with hetergogenous geographical or focal steatosis or with focal lesions of the liver such as haemagioma and focal nodular hyperplasia which can cause focal distortion of the liver echostructutre, and patients with ascites, patients with diseased or absent or ectopic right kidney.
Index test	Ultrasound EUB-8500 scanner with a 3.5 MHz phase-array convex transducer.The area of region of interest in the liver was between 3.5-4cm^2 and analysed for mean brightness level of each organ (liver and right kidney). The ratio between the mean brightness level of the liver and the right kidney was calculated manually to determine the hepatorenal sonographic index. In each case the calculation was repeated at least twice and when the difference was <0.20 the average was calculated. Applying the cut-off of 1.49 for the diagnosis of steatosis yielded a κ of 0.86 representing an excellent degree of agreement.
Reference standard	Simultaneous with ultrasound. Ultrasound guided biopsy performed with a Tru-Cut 1g-gauge needle. Specimens were fixed in formalin and embedded in paraffin. Examined by pathologist blinded to hepatorenal sonographic results. Liver steatosis classified as non ≤5%, mild 5-24% and moderate to severe ≥25%. And to diagnose massive fatty liver infiltration added classification of massive steatosis ≥60%
Target condition	Steatosis ≥5%
Results: 2x2 table calculated using author-reported raw data TP 45 FP 6 FN 0 TN 60 Sensitivity 100%	

Study	Webb 2009[1027]
Specificity 91% PPV 88% NPV 100% Area under the curve 0.992 (0.98–1.00) General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection. Unclear if index test interpreted without knowledge of reference standard results, and threshold not pre-specified.	

Study	Wu 2014[1046]
Study type	Prospective study
Number of studies (number of participants	1 (n=60)
Countries and Settings	Single centre, Taiwan
Funding	National Taiwan university Hospital grant
Duration of study	From August 2011 to October 2012
Age, gender, ethnicity	Mean age (range) 59.9 years (30-87). Male 75%. Ethnicity NR
Patient characteristics	Adults (20-99 years of age) with a hepatic tumour scheduled to undergo a liver resection. Exclusion criteria: history of haemochromatosis, liver resection, radiofrequency ablation, or transarterial embolization within 6 months, treatment with obvious hepatotoxic drugs within 1 month, contraindications to MRI or inability to suspend respiration for image acquisition. Main indications for liver resection: hepatocellular carcinoma 72%, cholangiocarcinoma 12%, other 16%.
Index test	MRI, MRS performed within 7 days of surgery using 3.0 Tesla unit. Double-echo IP/OP sequence was performed using a 20mm square region of interest with the same location as the voxel registered for MRS to measure SI on IP and OP images. The fat signal fraction in the double-echo sequence (FSF_{DE}) can be quantified as $FSF_{DE} = (SI_{IP} – SI_{OP})/2SI_{IP}$.The water-fat ambiguity was not corrected because only single-flip angle was used. The TE-MRI performed through the liver was breath-hold low-flip-angle T1-weighted 3D triple-echo spoiled gradient-echo sequence. The T2* map, water image, fat image, and fat fraction map were derived from the triple-echo spoiled

Study	Wu 2014[1046]		
	gradient-echo sequence by using pixel-by-pixel image calculations for each section under the following equation FSF_{TE} = $(SI_{IP1} – SI_{OP}*SI_{IP2}^{1/2}/SI_{IP1})/2SI_{IP1}$. A square ROI with the same size and location in double-echo sequence in the fat signal fraction map was chosen, and the fat signal fraction in the triple-echo sequence (FSF_{TE}) was obtained. A high-speed T2-corrected multi-echo proton MRS was also provided. MRS spectra obtained using voxel size of 20x20x20 mm was obtained at the normal liver parenchyma within the planned hepatic resection for the hepatic tumour. Each MRS acquisition was completed during a single breath-hold (15S). Operator involvement was minimised using automated shimming and post-processing procedures. The far percentage was the fat signal fraction as determined with MRS (FSF_{MRS}). Optimal cut-off determined by ROC curve: DE-MRI 11.08%, TE-MRI 5.35%, MRS 4.73%		
Reference standard	Wedge biopsy from part of the resected liver during surgery. Non-tumour liver tissue sizes 1-12cm^2 containing at least 120 portal triads was evaluated for steatosis and fibrosis. Steatosis graded using NASH-CRN: S0 <5%, S1 5-33%, S2 33-66%, S3 >66%.		
Target condition	Steatosis >5%		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **DE-MRI** TP 12 FP 10 FN 2 TN 36 Sensitivity 86% Specificity 78% PPV 54.5% NPV 95% Area under the curve 0.8773	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **TE-MRI** TP 13 FP 2 FN 1 TN 44 Sensitivity 93% Specificity 96% PPV 87% NPV 98% Area under the curve 0.9783	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **MRS** TP 13 FP 8 FN 1 TN 38 Sensitivity 93% Specificity 83% PPV 62% NPV 97% Area under the curve 0.9464	
General limitations according to QUADAS II: Unclear if index test interpreted without knowledge of reference standard results, and threshold not pre-specified.			

Study	Yajima 1983[1054]
Study type	Retrospective evaluation of abdominal echograms
Number of studies (number of participants	1 (n=45)
Countries and Settings	Japan
Funding	Prospective cohort
Duration of study	Not reported
Age, gender, ethnicity	Not reported
Patient characteristics	Liver disease aetiology: NAFLD 22%, cirrhosis 38%, chronic hepatitis 15%, acute hepatitis 2%, primary sclerosing cholangitis 2%, non-specific reactive hepatitis 18% and normal liver 2%
Index test	Commercially available grey scale ultrasonoscopes equipped with a long internally focused 3.5 MHz transducer. Right intercostal scan demonstrated the right lobe and the right kidney on the same plane for contrast. Vascular blurring (blurring of the hepatic vein trunk) and deep attenuation (attenuation of the echo-beam in deep portion of the right hepatic lobe) were evaluated on the right subcostal scans by representing the right hepatic lobe and the hepatic vein trunk. Ultrasound performed within two weeks prior to biopsy.
Reference standard	Liver biopsy Fatty changes subdivided into low grade <30%, moderate grade 30-50%, and high grade >50%
Target condition	Fatty change of >30% in the hepatic lobule
Results: 2x2 table calculated using author-reported raw data TP 10 FP 0 FN 2 TN 33 Sensitivity 83% Specificity 100% PPV 100%	

Study	Wu 2014[1046]
NPV 94% Area under the curve NR General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection. Unclear index test threshold.	

Study	Yajima 1983[1054]
Study type	Retrospective evaluation of abdominal echograms
Number of studies (number of participants	1 (n=45)
Countries and Settings	Japan
Funding	Prospective cohort
Duration of study	Not reported
Age, gender, ethnicity	Not reported
Patient characteristics	Liver disease aetiology: NAFLD 22%, cirrhosis 38%, chronic hepatitis 15%, acute hepatitis 2%, primary sclerosing cholangitis 2%, non-specific reactive hepatitis 18% and normal liver 2%
Index test	Commercially available grey scale ultrasonoscopes equipped with a long internally focused 3.5 MHz transducer. Right intercostal scan demonstrated the right lobe and the right kidney on the same plane for contrast. Vascular blurring (blurring of the hepatic vein trunk) and deep attenuation (attenuation of the echo-beam in deep portion of the right hepatic lobe) were evaluated on the right subcostal scans by representing the right hepatic lobe and the hepatic vein trunk. Ultrasound performed within two weeks prior to biopsy.
Reference standard	Liver biopsy Fatty changes subdivided into low grade <30%, moderate grade 30-50%, and high grade >50%
Target condition	Fatty change of >30% in the hepatic lobule
Results: 2x2 table calculated using author-reported raw data	

Study	Yajima 1983[1054]
TP 10 FP 0 FN 2 TN 33 Sensitivity 83% Specificity 100% PPV 100% NPV 94% Area under the curve NR General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection. Unclear index test threshold.	

H.3 Diagnosing the severity of NAFLD

Study	Adams 2011[13]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=242)
Countries and Settings	Australia, Italy; multi-centre study (hepatology units at 3 centres; 2 in Australia, 1 in Italy)
Funding	Study was funded by the Ada Bartholomew Medical Research Trust (University of Western Australia); one author was supported by the Robert W Storr Bequest and the National Health and Medical Council of Australia
Duration of study	NR
Age, gender, ethnicity	Mean age (SD): 46.8 (12.4), 60.3% Male. Ethnicity NR
Patient characteristics	Mean BMI of 30.2 kg/m^2 (SD 6.2), 41% were obese (BMI ≥ 30 kg/m^2), approximately 25% had diabetes. Exclusions/exclusion criteria: if patients consumed more than 210g of alcohol (male) or 140g (female) per week; if patients had secondary causes of NAFLD such as corticosteroid and methotrexate use or previous gastro-intestinal

Study	Adams 2011[13]		
	bypass surgery. Concomitant viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, alpha-1 anti-trypsin deficiency, Wilson's disease, hemochromatosis, drug induced hepatotoxicity were excluded by routine serological, imaging and histological criteria. 28 patients were excluded because of a suboptimal biopsy (13), daily alcohol intake > 30g (2), incomplete biochemical data (6), features of chronic cholestatic liver disease on biopsy (1)		
Index test	Noninvasive algorithm's calculated from the following components: Fibrotest (age, gender, bilirubin, GGT, apolipoprotein A1, haptoglobin, α-2 macroglobulin) APRI: [AST/(upper limit of normal AST)/platelet count (10^9/L)]*100 BARD (BMI, AST, ALT, diabetes) FIB4 (age, AST, ALT, platelets)		
Reference standard	Liver biopsies were scored by a single histopathologist at each centre blinded to the clinical details of the patients. The median (range) biopsy length was 16.0mm (6-50mm). Six patients were excluded due to biopsies determined inadequate for histological assessment.		
Target condition	Advanced fibrosis		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut-off 0.54** TP 38 FP 43 FN 15 TN 146 Sensitivity 72% Specificity 77%	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 32 FP 54 FN 21 TN 135 Sensitivity 60% Specificity 71%	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 1.54** TP 39 FP 25 FN 14 TN 164 Sensitivity 74% Specificity 87%	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Fibrotest: cut-off 0.47** TP 32 FP 19 FN 21 TN 170 Sensitivity 60% Specificity 90%

Study	Adams 2011[13]		
Area under the curve 0.788 (0.713-0.863)	Area under the curve 0.701 (0.619-0.783)	Area under the curve 0.858 (0.797-0.919)	Area under the curve 0.802 (0.727-0.876)
General limitations according to QUADAS II: It is unclear if patients were enrolled consecutively. Unclear if index test interpreted without knowledge of reference standard results. No information on the time between index test and the liver biopsy is given although it does mention serum markers were taken from the patients at the time of liver biopsy. Index tests cut-offs determined by highest Youden's index, not predetermined.			

Study	Aida 2014[20]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=116)
Countries and Settings	Japan; single-centre study at a university medical centre in Tokyo
Funding	Not reported
Duration of study	Jan 2010 – Dec 2013
Age, gender, ethnicity	Mean age (range): 61 (27-82), 35% Male. Ethnicity: Japanese
Patient characteristics	Patients admitted to medical centre for liver biopsies with NAFLD diagnosed using: ALT levels >30 U/L persisting for more than 6 months, no consumption of alcohol or hepatotoxic drugs, presence of hepatic steatosis on US or cirrhosis without steatosis on a liver biopsy where steatosis was indicated in the past, negative results for hepatitis B virus

Study	Aida 2014[20]
	surface antigen / high titer of hepatitis B virus core antibodies / anti-hepatitis C virus antibodies, absence of abnormal serum ceruloplasmin levels and transferrin saturation ratios. Mean BMI (range) 27.2 kg/m2 (18.8-45.9)
Index test	CK18-F: serum-level of CK18-F measured using the M30-Apoptosense ELISA kit.
Reference standard	US-guided liver biopsy performed at 2 different sites in the same lobe using a 16-gauge needle. The lengths of the sum of biopsy specimens were more than 1.8cm. A 10% neutral formalin solution was used for fixation and biopsy specimens were embedded in paraffin blocks. Sections were cut at 4 micrometre thickness stained by the hematoxylin-eosin and Masson trichrome. The median number (range) of portal tracts found in each sample was 10 (7-12).
Target condition	NASH
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK -18 [M30]: cut-off 270 U/L** TP 33 FP 16 FN 18 TN 49 Sensitivity 65% Specificity 75% Area under the curve 0.757 (0.667-0.846)	
General limitations according to QUADAS II: it is unclear if patients were enrolled consecutively. Histopathological assessment and scoring was done in a 'blinded fashion' though it is not clear whether index test results were interpreted without knowledge of the biopsy outcome. It is stated in the paper that fasting blood samples were obtained early in the morning of the day of the liver biopsy. Cut-off used was determined for 'optimal accuracy' not predefined.	

Study	Angulo 2007[67]
Study type	Prospective cohort

Study	Angulo 2007[67]
Number of studies (number of participants)	2 (construction n=480; validation n=253). Validation population included in this review.
Countries and Settings	Australia, Italy, UK and US ; multi-centre study.
Funding	Not reported
Duration of study	2000-2003
Age, gender, ethnicity	Mean age (SD): 47.7 (13.6). 49% Male. Ethnicity: 92% Caucasian
Patient characteristics	People with well-characterised and liver biopsy-proven untreated NAFLD. NAFLD diagnosis based on elevated AST and/or ALT, biopsy showing at least 10% steatosis, and appropriate exclusion of liver disease of other aetiology including alcohol-induced or drug-induced, autoimmune or viral hepatitis, and cholestatic or metabolic/genetic liver disease. Patients with clinical or imaging evidence of decompensated cirrhosis were specifically excluded from this study because they most likely had cirrhotic-stage NAFLD regardless of what a model may predict. Mean BMI (SD) 32.8 kg/m2 (6.7). 66% obese.
Index test	NAFLD fibrosis score -1.678 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x IFG/diabetes (yes=1, no=0) + 0.99 x AST/ALT ratio – 0.013 x platelet (10^9/1) – 0.66 x albumin (g/dl).
Reference standard	Liver biopsy stained with hematoxylin and eosin, Masson's trichome, and special stains for iron and copper. Liver biopsies were read by a single liver pathologist in each participating centre. To control for biopsy size, the length of the biopsy was measured with a hand ruler and the number of portal areas on one cross-section was counted. Mean (SD) length of biopsy was 18.1 (8.8)mm. The number of portal areas was 10.1 (4.5).
Target condition	Advanced fibrosis

Study	Angulo 2007[67]	
Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off -1.455** TP 57 FP 52 FN 17 TN 127 Sensitivity 77% Specificity 71% Area under the curve 0.82 (0.76-0.88)		Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off 0.676** TP 32 FP 7 FN 42 TN 172 Sensitivity 43% Specificity 96% Area under the curve 0.82 (0.76-0.88)
General limitations according to QUADAS II: Patients were enrolled consecutively. Unclear whether index test results were interpreted without knowledge of the biopsy outcome. Clinical and laboratory data were collected on the date of diagnostic liver biopsy. Cut-off used was determined by optimising PPV and NPV using thresholds based on previous estimation study.		

Study	Angulo 2014[66]
Study type	Retrospective analysis of medical records
Number of studies (number of participants)	1 (n=1014)
Countries and Settings	International multi-centre study: 4 university medical institutions (UK, Australia, Italy, and US)
Funding	The study was supported by a National Institute of Health grant, the FP7, and grants from the NHMRC.
Duration of study	Not reported
Age, gender, ethnicity	Mean age: 46.9 (0.4). 58% Male. Ethnicity: White (n=929), Asian (n=61), Black (n=7), American Indian/Alaska Native (n=2), Native Hawaiian or Other Pacific Islander (n=15)
Patient characteristics	Well-characterised and liver biopsy-confirmed untreated NAFLD patients.

Study	Angulo 2014[66]		
	Mean BMI: 31.3 kg/m2 (±0.2), 29% had diabetes, 38%had metabolic syndrome, 59% had central obesity Exclusions/exclusion criteria: liver disease of other aetiology (such as alcohol-induced or drug-induced liver disease, autoimmune or viral hepatitis, cholestatic or metabolic/genetic liver disease), weekly alcohol consumption of ≥210 g (male) or ≥140 g (female)		
Index test	Serum Ferritin levels measured by enzyme-linked immunosorbent assays or enzyme immunoassays as recommended by the WHO. The upper normal limit (UNL) for serum ferritin used for comparisons was adopted from the hemochromatosis and iron overload screening study: 300ng/mL in men and 200ng/mL in women.		
Reference standard	Liver biopsy: the mean length of the liver biopsy was 19mm (±8.5), the number of portal areas was 11 (±4.5). The biopsies were routinely stained with hematoxylin and eosin, Masson's trichrome, and special stains for iron and copper.		
Target condition	Any fibrosis and advanced fibrosis		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Ferritin – any fibrosis: 1 x UNL** TP 245 FP 84 FN 418 TN 267 Sensitivity 37% Specificity 76% Area under the curve 0.57 (0.53-0.60)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Ferritin – any fibrosis: 1.5 x UNL** TP 146 FP 39 FN 517 TN 312 Sensitivity 22% Specificity 89% Area under the curve 0.55 (0.52-0.59)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Ferritin – any fibrosis: 2 x UNL** TP 86 FP 18 FN 577 TN 333 Sensitivity 13% Specificity 95% Area under the curve 0.54 (0.50-0.58)	

Study	Angulo 2014[66]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Ferritin – advanced fibrosis: 1 x UNL** TP 111 FP 223 FN 160 TN 520 Sensitivity 41% Specificity 70% Area under the curve 0.55 (0.51-0.59)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Ferritin – advanced fibrosis: 1.5 x UNL** TP 73 FP 119 FN 198 TN 624 Sensitivity 27% Specificity 84% Area under the curve 0.56 (0.52-0.60)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Ferritin – advanced fibrosis: 2 x UNL** TP 43 FP 59 FN 228 TN 684 Sensitivity 16% Specificity 92% Area under the curve 0.54 (0.50-0.58)	
General limitations according to QUADAS II: There was a single liver pathologist in each participating centre who analysed the biopsies. Clinical and laboratory data were collected within 7 days of the liver biopsy procedure. Unclear whether the people interpreting the lab tests were blind to liver biopsy results. Cut-offs determined by logistic regression as optimising rule in and rule out – not predefined.			

Study	Chan 2014[184]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=93)
Countries and Settings	Malaysia, single centre university medical centre.
Funding	Funded by the University of Malaya Research Grant.
Duration of study	November 2012 to October 2013
Age, gender, ethnicity	Mean age: 51.0 (11.1). 52% Male. Ethnicity: NR
Patient characteristics	Recruited consecutively from adults (≥18) with NAFLD scheduled for a liver biopsy. Diagnosis of NAFLD was based on

Study	Chan 2014[184]	
	ultrasonography finding of fatty liver and exclusion of significant alcohol intake, use of medications that can cause fatty liver, viral hepatitis B and C infection, and other causes of chronic liver disease.	
Index test	ALT (upper limit of normal 65 IU/L) CK 18 M30 collected on same day as liver biopsy. Quantitative measurement using the M30 Apoptosense ELISA kit. Performed for all samples in a single session by a single investigator.	
Reference standard	Liver biopsy: ultrasonography-guided percutaneous liver biopsy using an 18 gauge Temno 11 semi-automatic biopsy needle. Stained with hematoxylin and eosin stain and Masson's trichome.	
Target condition	NASH	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: cut-off 53** TP 31 FP 32 FN 8 TN 22 Sensitivity 80% Specificity 41% Area under the curve 0.64 (0.53-0.76)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: cut-off 67** TP 28 FP 22 FN 11 TN 32 Sensitivity 72% Specificity 59% Area under the curve 0.64 (0.53-0.76)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: cut-off 100** TP 16 FP 11 FN 23 TN 43 Sensitivity 41% Specificity 80% Area under the curve 0.64 (0.53-0.76)

Study	Chan 2014[184]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 293** TP 28 FP 32 FN 11 TN 22 Sensitivity 72% Specificity 41% Area under the curve 0.59 (0.47-0.71)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 432** TP 22 FP 20 FN 17 TN 34 Sensitivity 56% Specificity 63% Area under the curve 0.59 (0.47-0.71)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 474** TP 17 FP 19 FN 22 TN 35 Sensitivity 44% Specificity 65% Area under the curve 0.59 (0.47-0.71)	
General limitations according to QUADAS II: Clinical and laboratory data were collected on same day as the liver biopsy procedure. Unclear whether the people interpreting the lab tests were blind to liver biopsy results. Cut-offs were not pre-specified.			

Study	Cichoz-Lach 2012[210]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=126)
Countries and Settings	Single-centre Gastroenterology division of an university medical centre in Lublin, Poland.
Funding	Departmental sources
Duration of study	Not reported
Age, gender, ethnicity	Mean age: 42.7 (±13.94), 58% Male. Ethnicity: ethnically homogenous Caucasian group of patients

Study	**Cichoz-Lach 2012[210]**	
Patient characteristics	Diagnosis of NAFLD was based on elevated ALT and AST and liver biopsy showing steatosis in at least 5% of hepatocytes and alcohol intake lower than 20g/day in women and 30g/day in men. Mean BMI: 28.51 kg/m^2 (±2.67), 19% were obese, 23% had diabetes Exclusions/exclusion criteria: HBV, HCV, autoimmune liver disease, primary liver cirrhosis, Wilson's disease, hemochromatosis, drug-induced liver disease, other causes of chronic liver disease	
Index test	NAFLD fibrosis score: -1.675 + 0.037 – age (years) + 0.094 – BMI + 1.13 * IFG/diabetes (yes = 1, no = 0) + 0.99 * AST/ALT ratio – 0.013 * platelet count (*10^9/L) – 0.66 * albumin (g/dL) BARD score composed of 3 variables (score ranges from 0 to 4 points): AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point.	
Reference standard	Liver biopsy: no details are reported	
Target condition	Advanced fibrosis	
Results: 2x2 table calculated using author-reported raw data **Bard: cut-off 2** TP 24 FP 11 FN 3 TN 88 Sensitivity 89% Specificity 89% Area under the curve 0.865 (0.793-0.920)	Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off -1.455** TP 24 FP 10 FN 3 TN 89 Sensitivity 96% Specificity 53% Area under the curve 0.919 (0.841-0.967)	Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off 0.676** TP 26 FP 47 FN 1 TN 52 Sensitivity 89% Specificity 90% Area under the curve 0.919 (0.841-0.967)
General limitations according to QUADAS II: It is unclear whether patients were enrolled consecutively. No details on liver biopsy. All liver biopsies were evaluated by the same liver pathologist, though it is unclear whether the pathologist was blind to the results of the index test. Variables necessary for the assessment scores and laboratory analysis were determined the day before the liver biopsy. Thresholds based on previously published cut-offs.		

Study	Cui 2015 [228]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=102)
Countries and Settings	Single centre university research unit, USA
Funding	Funding provided by Atlantic Philanthropies, Inc, the John A. Hartford Foundation, the Association of Specialty Professors, and the American Gastroenterological Association.
Duration of study	May 2012 to October 2014
Age, gender, ethnicity	Mean age (SD): 51.3 (14.0); Sex 58.8% female; Ethnicity: 53% White, 15.7% Asian, 28.4% Hispanic, 2% multiracial, 1% other, 1% missing
Patient characteristics	Adults ≥18 years with biopsy confirmed NAFLD Exclusion criteria: regular and/or excessive alcohol use within 2 years prior to recruitment (≥14 drinks/week if make or ≥7 drinks/week if female); clinical or laboratory evidence of secondary NAFLD due to major nutritional and iatrogenic gastrointestinal disorders or HIV infection; clinical or laboratory evidence of non-NAFLD liver diseases including hepatitis B, hepatitis C, hemochromatosis, Wilson's disease, glycogen storage, alpha-1 antitrypsin deficiency, autoimmune hepatitis, cholestatic liver disease and vascular liver disease, clinical or laboratory evidence of decompensated liver disease; active substance abuse, significant systemic illnesses; pregnant status or attempting to become pregnant; contraindication to MRI.
Index test	2D-MRE: While vibrations are being transmitted at 60 Hz, a 2D gradient-recalled echo MRE pulse sequence is performed, and 4 non-contiguous axial slices (10 mm thick, 10mm inter-slice gap) are acquired in 16-s breath holds at the widest transverse part of the liver. The acquisition parameters include repetition time (TR), 50ms; echo time (TE), 20.2 ms; flip angle, 30°; matrix 256 x 64; field of view 48 x 48cm; one-signal average, receiver bandwidth ± 33 kHz; and parallel imaging acceleration factor 2. The total acquisition time is about 2 mins with 4 x 16-s breath holds with short recovery in between. After data acquisition four quantitative cross-sectional maps (elastograms) are generated, depicting tissue stiffness at each of the four slice locations using a colour scale in units of kilopascals (kPa). The image analyst manually drew regions of interest (ROIs) on the elastograms at the four slice locations in parts of the liver where corresponding wave images showed clearly observable wave propagation, while avoiding liver edges, large blood vessels, and artefacts. The per-pixel stiffness values across the ROIs at the four slice locations were averaged to calculate the mean 2D-MRE stiffness.

Study	**Cui 2015** [228]		
	Clinical prediction rules: AST/ALT ratio, APRI, BARD, FIB4 and NAFLD fibrosis score all calculated from laboratory assessment data (previously published formulas and thresholds). Only results for FIB4 reported.		
Reference standard	Liver biopsy read and scored by an experienced liver pathologist blinded to radiological data. NASH CRN scoring system used.		
Target condition	Advanced fibrosis		
Results: 2x2 table calculated using author-reported raw data **2D MRE: cut-off 3.64 kPa** TP 17 FP 8 FN 2 TN 75 Sensitivity 92% Specificity 90% PPV 68% NPV 98% Area under the curve 0.957 (0.918-0.996)	Results: 2x2 table calculated using author-reported raw data **FIB4: cut-off 1.30** TP 16 FP 24 FN 3 TN 59 Sensitivity 84% Specificity 72% PPV 41% NPV 95% Area under the curve 0.861 (0.775-0.946)	Results: 2x2 table calculated using author-reported raw data **FIB4: cut-off 2.67** TP 5 FP 2 FN 14 TN 81 Sensitivity 25% Specificity 98% PPV 70% NPV 85% Area under the curve 0.861 (0.775-0.946)	
General limitations according to QUADAS II: It is unclear if patients were enrolled consecutively. Unclear if index test interpreted without knowledge of reference standard results. Median time interval between biopsy and clinical assessment was 29 days. The median time interval between biopsy and 2D-MRE was 41 days.			

Study	**Cusi 2014**[229]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=318)

Study	Cusi 2014[229]
Countries and Settings	General medicine or hepatology clinics at University of Texas or Brooke Army Medical Center, USA.
Funding	Multiple government / not for profit funding sources: Burroughs Wellcome Fund, American Diabetes Association, VA Merit Award, NIH grant, Veterans Affairs Medical Research Fund and the National Centre for Research Resources.
Duration of study	Not reported
Age, gender, ethnicity	Age - without NASH 53 (1), with NASH 52 (1) (mean (SD)); Sex (male) - without NASH 64%, with NASH 65%; ethnicity not reported.
Patient characteristics	N=119 without NASH, 199 with NASH, All subjects were overweight / obese at recruitment. BMI was significantly different in those with / without NASH; 32.8 (1.1) in those without NASH and 33.6 (0.6) in those with NASH P=0.01. Exclusions/exclusion criteria: No evidence of any serious chronic disease (other than NAFLD, type II diabetes mellitus and associated comorbidities). Volunteers were excluded if they had a history of alcohol abuse (≥20 grams/day; all underwent an AUDIT questionnaire), liver disease other than NASH (i.e. hepatitis B/C, autoimmune hepatitis, hemochromatosis, other), type I diabetes mellitus or clinically significant renal/pulmonary/heart disease.
Index test	Subjects were admitted to the research unit at 6:30-7:00 am after a 12-hour overnight fast. Plasma CK-18 levels – Samples were placed on ice at the bedside, processed within 15-20 mins and frozen at -80 °C until final analysis. CK-18 concentration was determined by the one-step in vitro immunoassay M30-apoptosense ELISA kit (PEVIVA AB; DiaPharma, OH) that selectively recognizes the capase cleavage-generated against the K18Asp396 neoepitope of CK-18.
Reference standard	Liver biopsy: A biopsy was performed in patients with elevated liver transaminasis when all other causes of liver disease were ruled out, or with normal liver transaminases if NAFLD by MRS was present in association with well-known risk factors for NASH such as type II diabetes mellitus, Metaboloic syndrome or insulin resistance as established during an OGTT (Matsuda index) and/or by a euglycemic insulin clamp.
Target condition	NASH
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 212 U/L** TP 115 FP 38 FN 84	

Study	Cusi 2014[229]
TN 81 Sensitivity 58% Specificity 68% Area under the curve 0.65 (0.59-0.71)	
General limitations according to QUADAS II: Assumed consecutively recruited, but not specifically stated – all patients recruited from the army medical centre had a liver biopsy, but at the University of Texas liver biopsy wasn't done if NAFLD wasn't present on MRS, normal aminotransferases or if the patient declined. 424 people studied, 300 of which had NAFLD (MRS diagnosed n=229, biopsy diagnosed n=66 and 5 positive ultrasound). 124 did not have NAFLD. Liver biopsy done in 318 participants, or which 199 had NASH. – NB flow chart available in a supplementary figure if required (not attached to paper). Biopsies were evaluated by an experienced pathologist that was unaware of the subject's identity or clinical information; although no information on whether index tests were interpreted without knowledge of the reference standard results. No details of time period between index test and reference standard being carried out.	

Study	Demir 2013[251]
Study type	Retrospective analysis of medical data
Number of studies (number of participants)	2 (n =267 recruited for estimation (n=170) validation (n=97) of a novel non-invasive tool not included in this review. Total population used for review index tests.)
Countries and Settings	Germany, multi-centre. 2 Gastroenterology and Hepatology clinics at 2 university hospitals.
Funding	No funding to report
Duration of study	Data collected from patients who presented to the clinics between July 1998 and November 2009.
Age, gender, ethnicity	Mean age (SD): 43.8 (12.1). Male 47%. Ethnicity NR
Patient characteristics	68.5% of patients referred to outpatient department for further work-up after abnormal liver function tests detected by their primary care physicians. A diagnosis of NAFLD made if the following conditions were met: elevated AST levels for at least 6 months, fatty liver degeneration >5% after exclusion of other chronic liver diseases (viral hepatitis, autoimmune disease, toxic liver injury, alcoholic steatohepatitis, cholestatic liver disease, hemochromatosis. Patients were excluded if they suffered from a malignancy, had decompensated liver cirrhosis or received drugs with well-known effects on steatosis. They were also excluded if the time interval between liver biopsy and date of lab examination exceeded 120 days or if data to definitely exclude chronic liver disease was missing. Patients included if

Study	Demir 2013[251]		
	alcohol consumption <30g/day in men and <20g/day in women. 141/408 excluded. Mean BMI (SD) 37 (12.7). 52% obese.		
Index test	AST/ALT ratio BARD NAFLD fibrosis score		
Reference standard	Liver biopsy: All specimens taken under local anaesthesia with a 17-gauge Menghini needle. Liver biopsies read twice by two experienced pathologists who were blinded in clinical and laboratory data.		
Target condition	Advanced fibrosis.		
Results: 2x2 table calculated using author-reported raw data **AST/ALT ratio: cut-off 0.8** TP 6 FP 162 FN 10 TN 82 Sensitivity 38% Specificity 34% Area under the curve 0.81 (0.72-0.90)	Results: 2x2 table calculated using author-reported raw data **AST/ALT ratio: cut-off 1** TP 14 FP 38 FN 8 TN 206 Sensitivity 64% Specificity 84% Area under the curve 0.81 (0.72-0.90)	Results: 2x2 table calculated using author-reported raw data **BARD: cut-off 2** TP 14 FP 101 FN 6 TN 121 Sensitivity 70% Specificity 55% Area under the curve 0.67 (0.55-0.78)	
Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off -1.455** TP 12 FP 7 FN 4 TN 97	Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off 0.676** TP 3 FP 0 FN 13 TN 104		

Study	Demir 2013[251]	
	Sensitivity 75% Specificity 93% Area under the curve 0.96 (0.92-0.99)	Sensitivity 19% Specificity 100% Area under the curve 0.96 (0.92-0.99)
General limitations according to QUADAS II: Consecutively included patients but retrospective nature of the design leads to concerns around patient selection. Not all patients included in analysis due to missing index test results (AAR=266, BARD=242, NAFLD fibrosis score=120). Cut-offs based on previously published thresholds. No information on whether index tests were interpreted without knowledge of the reference standard results. No details of time period between index test and reference standard being carried out although patients were excluded if this interval was longer than 120 days.		

Study	Dvorak 2014[266]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=56)
Countries and Settings	Prague, single-centre university hospital.
Funding	Supported by grants given by Internal Grant Agency, Czech Ministry of Health and from Charles University, Prague.
Duration of study	2010-2013
Age, gender, ethnicity	Mean age (SD): NASH 46.4 (15), non-NASH 43.6 (16). Gender NR. Ethnicity NR
Patient characteristics	Only includes 56/112 with NAFLD confirmed by liver biopsy. Those who were not indicated for biopsy not included. Viral hepatitis, drug-induced liver disease, autoimmune liver disease, biliary disease and inherited metabolic diseases were excluded by specific laboratory and radiologic examinations and by the patient history. Alcohol abuse was excluded by the patient history.
Index test	M30 and M65 levels were measured by commercially available ELISA tests. APRI calculated as: AST (IU/L/upper AST limit/platelet count ($x10^9$/L) x 100 FIB4 according to formula: age x AST(IU/L/upper AST limit/platelet count ($x10^9$/L) x ALT (IU/l) NAFLD fibrosis score: -1.678 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x impaired glucose tolerance or diabetes

Study	Dvorak 2014[266]		
	(yes=1, no=0) + 0.099 x AST/ALT ratio – 0.013 x platelet (10^9/1) – 0.66 x albumin (g/dl). BARD: composed of 3 variables (score ranges from 0 to 4 points): AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point. ELF calculated using algorithm: -7.412 + (ln(HA) x 0.681) + (ln(PIIINP) x 0.775) + (ln(TIMP-1) x 0.494		
Reference standard	Liver biopsy: in 43 patients conducted by the percutaneous method with a Menghini needle and in the other 13 patients by transjugular method. The indications for transjugular were obesity, thrombocytopenia, suspicion of liver cirrhosis, and the need for a hepatic venous pressure gradient measurement. The biopsy samples were routinely stained and then read by a single pathologist blind to the clinical and laboratory data.		
Target condition	NASH Advanced fibrosis.		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NASH** **CK-18 [M30]: cut-off 234 U/L** TP 29 FP 3 FN 9 TN 15 Sensitivity 76% Specificity 83% Area under the curve 0.85 (0.50-0.92)	Results: 2x2 table calculated using using author-reported sens, spec and study prevalence **NASH** **CK-18 [M65]: cut-off 790 U/L** TP 30 FP 3 FN 8 TN 15 Sensitivity 79% Specificity 83% Area under the curve 0.89 (0.48-0.93)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NASH** **ALT: cut-off 1.02 µkat** TP 27 FP 7 FN 11 TN 11 Sensitivity 71% Specificity 61% Area under the curve NR	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **APRI: cut-off 0.65** TP 11 FP 13 FN 6	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **AST/ALT ratio: cut-off 0.67** TP 11 FP 13 FN 6		

Study	Dvorak 2014[266]		
TN 926 Sensitivity 65% Specificity 67% Area under the curve 0.70 (0.40-0.79)		TN 26 Sensitivity 65% Specificity 67% Area under the curve 0.73 (0.44-0.82)	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **ELF score: cut-off -3.37** TP 15 FP 1 FN 2 TN 38 Sensitivity 88% Specificity 97% Area under the curve 0.97 (0.51-0.99)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **FIB4: cut-off 1.51** TP 12 FP 9 FN 5 TN 30 Sensitivity 71% Specificity 77% Area under the curve 0.83 (0.50-0.87)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **NAFLD fibrosis score: cut-off -2.16** TP 13 FP 12 FN 4 TN 27 Sensitivity 76% Specificity 69% Area under the curve 0.81 (0.54-0.92)	
General limitations according to QUADAS II: Consecutively included patients. Unclear how thresholds determined. Unclear whether index test results interpreted without knowledge of biopsy outcomes and unclear interval between index tests and reference standard.			

Study	Feldstein 2009[300]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=139)
Countries and Settings	8 NASH clinical research network centres, USA
Funding	Nonalcoholic Steatoheaptitis Clinical Research Network, General Clinical Research Center Grant and NIH.

Study	Feldstein 2009[300]	
Duration of study	Not reported	
Age, gender, ethnicity	Age median 48 years (39 – 55), sex 63% female, 79% Caucasian	
Patient characteristics	BMI median 34 kg/m^2 Inclusion / Exclusion criteria: Adults with NAFLD n=139, defined by: liver biopsy features as assessed by NASH CRN pathologists; appropriate exclusion of liver disease of other etiologies including alcohol- or drug-induced, autoimmune, viral, cholestatic, metabolic or genetic disorders; and plasma sample available within 3 months of baseline liver biopsy.	
Index test	Capase-generated CK-18 fragments in the blood – for all patients, a blood sample was taken within 3 months of the liver biopsy was obtained from the NIH blood bank repository. All samples were originally processed to plasma and stored at -80 °C. The plasma was subsequently used for quantitative measurement of the apoptosis-associated neo-epitope in the C-terminal domain of CK-18 by the M30-Apoptosense ELISA kit (LEVIVA< Bromma, Sweden). All assays were performed in duplicate, and the absorbance was determined using a microplate reader (Molecular Devices M2, Sunnyvale, CA).	
Reference standard	Histological diagnosis was established by study pathologists according to their expertise	
Target condition	NASH	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 216 U/L** TP 53 FP 24 FN 16 TN 46 Sensitivity 77% Specificity 66% Area under the curve 0.83 (0.61-0.78)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 287 U/L** TP 45 FP 6 FN 24 TN 64 Sensitivity 70% Specificity 95% Area under the curve 0.83 (0.61-0.78)	

Study	Feldstein 2009[300]
General limitations according to QUADAS II: No details of recruitment (NB – study in children says consecutively recruited so it is likely to be the same as they were the same initial cohort) but retrospective nature of the design leads to concerns around patient selection. No details of biopsy methods reported. Blood sample for index test taken within 3 months of biopsy. Unclear whether index test results were determined with/without knowledge of the reference standard. Confidence interval for the reported AUROC does not include the point estimate. Index tests thresholds not pre-specified.	

Study	Feldstein 2013[298]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=201)
Countries and Settings	Unclear – assumed to be 1 children's hospital in Italy
Funding	Grants from Bambino Gesu Children's Hospital and Research Institute, Rome, Italy and NIH.
Duration of study	Not reported
Age, gender, ethnicity	Age – mean 10.7 (2.5) years, sex - 37% male
Patient characteristics	Children with NAFLD Inclusion / Exclusion criteria: Persistently elevated serum aminotransferase levels, diffusely hyperechogenic liver on ultrasonography suggestive of fatty liver, and biopsy consistent with the diagnosis of NAFLD. Exclusion criteria were hepatic virus infections (hepatitis A, B, C, D and E, cytomegalovirus, and Epstein-Barr virus), alcohol consumption, history of parenteral nutrition, and use of drugs known to induce steatosis (e.g. valproate, amiodarone, or prednisone) or to affect body weight and carbohydrate metabolism. Autoimmune liver disease, metabolic liver disease, Wilson's disease, and α-1-antitrypsin-associated liver disease were ruled out.
Index test	CK-18 level measurements – for all patients, a blood sample was taken at the time of the liver biopsy. All samples were originally processed to yield plasma and stored at -80 °C. The plasma was subsequently used for quantitative measurement of CK-18 levels by the M30-Apoptosense ELISA kit (PEVIVA, Li Starfish, Italy). All assays were performed in duplicate, and the absorbance was determined using a microplate reader (Molecular Bio-Rad, Milan Italy).
Reference standard	Biopsy performed after an overnight fast using an automatic core biopsy 18-gauge needle (Biopince, Amnedic, Sweden) under general anaesthesia and ultrasound guidance. The length of liver specimen (in mm) was recorded. Only samples that were not fragmented with a length 15mm and including at least 6 complete portal tracts were considered

Study	Feldstein 2013[298]		
	adequate for the purpose of the study. Biopsies were routinely processed and sections of liver tissue, 5mm thick, were stained with hematoxylineosin, Van Gieson, Periodic acid-Schiff diastase, and Prussion blue stain.		
Target condition	NASH		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 218 U/L** TP 127 FP 15 FN 13 TN 46 Sensitivity 91% Specificity 75% Area under the curve 0.9335	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 233 U/L** TP 119 FP 8 FN 21 TN 53 Sensitivity 85% Specificity 87% Area under the curve 0.9335	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 268 U/L** TP 98 FP 3 FN 42 TN 58 Sensitivity 70% Specificity 95% Area under the curve 0.9335
General limitations according to QUADAS II: Consecutively recruited but retrospective nature of the design leads to concerns around patient selection. Biopsies were evaluated by a single expert paediatric hepatopathologist who established the histopathological diagnosis of NASH. Patients were then divided into 2 groups “NASH” and diagnosis not compatible with NASH or “not NASH”. Liver biopsy features for each case were also graded according to the NAFLD activity scoring system proposed by Kleiner et al. Blood samples for the index test were performed at the same time as the biopsy. Unclear whether index test results were determined with/without knowledge of the reference standard. Thresholds for index tests were not pre-specified. No confidence intervals reported for AUC despite reporting them for other serum biomarkers.			

Study	Goh 2015[355]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=503)
Countries and Settings	USA multi-centre study from two Hepatology outpatient clinics in Cleveland, Ohio.

Study	Goh 2015[355]		
Funding	No grant support funding		
Duration of study	Not reported		
Age, gender, ethnicity	Mean age (SD) 49 (12): Male 38%: Ethnicity NR		
Patient characteristics	Patients ≥18 years with histologically proven NAFLD who had not received any prior therapies that may have been beneficial for NAFLD, such as Vit E, pentoxifylline, pioglitazone and prescribed diet and exercise weight loss programmes. Patients with excessive alcohol consumption (>21 drinks per week for males and >14 drinks for females) were excluded. Similarly patients with other contributory causes of liver disease including those with hepatoxic drug history, viral hepatitis, hemochromatosis, autoimmune hepatitis, Wilson's disease or alpha 1 antitrypsin disease were excluded. Mean BMI 36.13 (8.43). 58% hypertension, 48% diabetes.		
Index test	AST/ALT ratio BARD: AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point. NAFLD fibrosis score: -1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x impaired fasting glycaemia or diabetes (yes=1, no=0) + 0.99 x AST/ALT ratio – 0.013 x platelet (10^9/L) – 0.66 x albumin (g/dl). Only clinical variables obtained within 6 months of the liver biopsy were included in analysis.		
Reference standard	No information about method of liver biopsy.		
Target condition	Advanced fibrosis		
Results: 2x2 table calculated using author-reported raw data **AST/ALT ratio: cut-off 0.8** TP 118 FP 124 FN 16 TN 224	Results: 2x2 table calculated using author-reported raw data **BARD: cut-off 2** TP 118 FP 197 FN 16 TN 150	Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off -1.455** TP 103 FP 168 FN 24 TN 166	Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off 0.676** TP 50 FP 26 FN 79 TN 308

Study	Goh 2015[355]		
Sensitivity 88% Specificity 64% Area under the curve NR	Sensitivity 88% Specificity 43% Area under the curve NR	Sensitivity 80% Specificity 50% Area under the curve NR	Sensitivity 39% Specificity 92% Area under the curve NR
General limitations according to QUADAS II: It is unclear if patients were enrolled consecutively. Unclear if index test interpreted without knowledge of reference standard results. Unclear how index tests cut-offs determined but presumed to be based on previously published cut-offs. No information provided about method of liver biopsy. Final numbers in index test tables do not represent initial population and no information on exclusion reasons.			

Study	Grigorescu 2012[363]
Study type	Diagnostic cohort (assumed prospective)
Number of studies (number of participants)	1 (n=79)
Countries and Settings	Romania, setting not reported
Funding	Not reported
Duration of study	Not reported
Age, gender, ethnicity	Age - Not NASH 39.1 (10.7), NASH 48.3 (11.4) years; Gender F/M – Not NASH 6/14, NASH 17/42; Ethnicity not reported
Patient characteristics	People with biopsy proven NAFLD. No patients had fasting glucose level >140 mg or underwent treatment with insulin. Inclusion / exclusion criteria: Liver biopsies were performed in those with abnormal liver function tests lasting for at least 6 months and suspected NAFLD at grey scale ultrasonography. Patients with other liver disease etiologies: hepatitis B or C, autoimmune liver disease, Wilson disease, hemochromatosis, αa-antitripsin deficiency, HIV infection, patients with a history of hepatotoxic or steatosis-inducing drugs or those with daily alcohol intake exceeding 10g/day for women and 20 g/day for men were excluded. Patients with a history of an inflammatory disease, current infection or history of cancer, as well as those receiving treatment with PPAR-γ agonists were also excluded.
Index test	Total CK-18 (M65 antigen) was determined by commercially available Kit (M65 ELISA, Peviva AG, Sweden) with a sensitivity of 11 U/L, according to the manufacturer's instructions. This method is based on the capture (M6) and

Study	Grigorescu 2012[363]
	detection (M5) of antibodies directed against two different epitopes of CK-18, independently of the cleavage status.
Reference standard	Biopsy: Liver biopsies were performed under ultrasonographic guidance and stained with meotoxilin-eosin and Masson's trichrome and were assessed by a senior hepatopathologist blinded to the clinical or biological characteristics of the patients.
Target condition	NASH
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M65]: cut-off 340** TP 47 FP 7 FN 12 TN 13 Sensitivity 79% Specificity 67% Area under the curve 0.791 (0.685-0.874)	
General limitations according to QUADAS II: Recruitment details not reported. Index and reference standard results interpreted without knowledge of each other, although operators were not blinded to the other clinical data. Index test samples were performed on the same day as biopsy. No information provided on how index test thresholds provided.	

Study	Guha 2008[366]
Study type	Assumed prospective
Number of studies (number of participants)	1 (n=192)
Countries and Settings	UK, two tertiary outpatient centres in Nottingham and Newcastle-upon-Tyne.
Funding	Authors include shareholders of iQur Ltd and have received grant income from Bayer/Siemens

Study	**Guha 2008**[366]	
Duration of study	Between October 2002 to December 2006	
Age, gender, ethnicity	Mean age (SD) 48.7 (12.5). Male 64%. Ethnicity NR	
Patient characteristics	Diagnosis of NAFLD based on elevated AST or ALT levels; appropriate exclusion of liver disease of other origin including alcohol-induced or drug-induced, autoimmune or viral hepatitis, or cholestatic or metabolic/genetic liver disease. Mean BMI (SD) 32.4 (5.7). 63% metabolic syndrome.	
Index test	ELF: DS = -7.412 + (ln(HA)*0.681) + (ln(P3NP)*0.775) + (ln(TIMPI)*0.494). ELF + NAFLD fibrosis score = -20.870 + 5.506*ELF (discriminant score) + 4.513*diabetes/IFG (yes=1, no=0) – 3.144 AST/ALT ratio – 0.058*BMI (kg/m^2) – 0.026*platelets (x10^9/L) + 0.639*alb (g/L) Serum biomarkers taken within three months of biopsy.	
Reference standard	Liver biopsy: assessed by two hepatologists. No details on biopsy method.	
Target condition	Any fibrosis and advanced fibrosis	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **ELF: cut-off -0.2070** TP 69 FP 16 FN 44 TN 63 Sensitivity 61% Specificity 80% Area under the curve 0.76 (0.69-0.83)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **ELF: cut-off 0.3576** TP 35 FP 15 FN 9 TN 133 Sensitivity 80% Specificity 90% Area under the curve 0.90 (0.84-0.96)	

Study	Guha 2008[366]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **ELF + NAFLD fibrosis score: cut-off -0.2826** TP 40 FP 6 FN 4 TN 142 Sensitivity 91% Specificity 96% Area under the curve 0.98 (0.96-1.00)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **ELF + NAFLD fibrosis score: cut-off 0.0033** TP 39 FP 2 FN 5 TN 146 Sensitivity 86% Specificity 99% Area under the curve 0.98 (0.96-1.00)
General limitations according to QUADAS II: Consecutive recruitment. No information on method of liver biopsy. Appropriate interval between biopsy and index tests, but unclear if serum information interpreted without knowledge of histological data. Unclear how thresholds determined, presumed to be optimal accuracy – not pre-specified.		

Study	Joka 2012[477]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=22 patients with NAFLD of a larger population of people with a range of chronic liver diseases, n=121)
Countries and Settings	Germany; setting is unclear.
Funding	Supported by the Deutsche Forschungsgesellschaft
Duration of study	Not reported
Age, gender, ethnicity	Data only provided for all 121 patients enrolled in the study (also includes patients with other causes of liver disease): Mean age (±SD): 46.5 (±1.2), 50.4% Male. Ethnicity NR
Patient characteristics	NR for specific NAFLD population.

Study	Joka 2012[477]	
Index test	Measurement of capase-generated neoepitope of CK-18: M30-Apoptosense ELISA according to manufacturers instructions. M65 and M65 EpiDeath ELISA to quantify both uncleaved and capase-cleaved CK-18. The M65 assay is based on the capture (M6) and detection (M5) antibodies that are directed against two different epitopes of CK-18 and recognised total CK-18.	
Reference standard	Liver biopsy at same time as blood withdrawal. No details provided.	
Target condition	NASH	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 149.5 U/L** TP 9 FP 3 FN 3 TN 7 Sensitivity 75% Specificity 70% Area under the curve 0.77 (0.57-0.97)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M65]: cut-off 386 U/L** TP 12 FP 2 FN 0 TN 8 Sensitivity 100% Specificity 80% Area under the curve 0.93 (0.82-1.0)
General limitations according to QUADAS II: it is unclear whether patients were enrolled consecutively and whether exclusions were appropriate as not information provided for specific NAFLD population. Liver biopsy specimens were assessed by the same pathologist but no biopsy method data supplied. It is unclear if the index tests were interpreted without knowledge of the biopsy outcome. Unclear how thresholds for index tests were determined – not pre-specified.		

Study	Kawamura 2013[499]
Study type	Retrospective analysis
Number of studies (number of	1 (n=29)

Study	Kawamura 2013[499]
participants)	
Countries and Settings	Single-centre study at an urban medical centre in Tokyo, Japan
Funding	Okinaka Memorial Institute for Medical Research, Japanese Ministry of Health
Duration of study	Jan 2011 – Jul 2012
Age, gender, ethnicity	Mean age (range): 59.5 (29-80), 73% Male. Ethnicity NR
Patient characteristics	All patients were diagnosed with NASH. Mean BMI (range): 25.8 kg/m^2 (20.8-37.9) Inclusion criteria: undergoing 3D-MRI within 1 year before histological examination; past daily alcohol intake of <20 g/d; negative for serum hepatitis C virus antibodies, hepatitis B surface antigen, antinuclear bodies, antimitochondrial antibodies; no underlying systemic autoimmune disease; no underlying metabolic diseases
Index test	APRI calculated using the formula: {[AST level/upper normal level (33 IU/L)]/[platelet count (10^9/L)]}*100 BARD score composed of 3 variables: score ranges from 0 to 4 points: AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point FIB4-index calculated using the formula: [age(years) * AST level]/[platelet count (10^9/L) * (ALT level)$^{1/2}$] 3D-MRI – all patients underwent whole-liver MR image screening for early hepatocellular carcinoma and to assess the extent of liver disease. Advanced fibrosis defined on the3D-MRI image showing diffuse irregularity of the surface of the liver (including diffuse small irregularities or large irregularities with areas of nodularity)
Reference standard	Liver biopsy: specimen obtained using a 14-gauge modified Vim-Silverman needle, 16-gauge core tissue biopsy needle or surgical resection. Specimens were fixed in 10% formalin. Sections were stained with hematoxylineosin, Masson trichrome, silver impregnation, and periodic acid-Schiff after diastase digestion. 20 of 30 patients underwent US-guided biopsy using a 16-gauge core tissue biopsy needle, 9 underwent laparoscopy0guided biopsy using a 14-gauge modified Vim-Silverman needle and 1 underwent surgical resection for hepatocellular carcinoma that had been found on 3D-MRI (excluded from analysis).
Target condition	Advanced fibrosis

Study	Kawamura 2013[499]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut-off 0.98** TP 6 FP 3 FN 2 TN 9 Sensitivity 78% Specificity 71% Area under the curve NR	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 7 FP 2 FN 1 TN 10 Sensitivity 78% Specificity 90% Area under the curve NR	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 2.67** TP 6 FP 2 FN 2 TN 11 Sensitivity 78% Specificity 90% Area under the curve NR	This information has been excluded from the review based on GDG consensus that the diagnostic criteria are too subjective and non-reproducible. **3D-MRI: cut-off "diffuse irregularity of the surface of the liver"** TP 8 FP 2 FN 0 TN 19 Sensitivity 100% Specificity 90% Area under the curve NR
General limitations according to QUADAS II: retrospective nature of the design leads to concerns around patient selection, especially as they are only being given MRI for suspicion of another liver disease (aside form NAFLD). It is unclear whether index tests were interpreted without knowledge of the biopsy outcome or vice versa. Patients had to undergo the 3D-MRI within 1 year before the liver biopsy. It is unclear at what time the other index tests were performed. Thresholds pre-specified and determined from published cut-offs.			

Study	Khosravi 2011[505]
Study type	Retrospective study
Number of studies (number of participants)	1 (n=147)
Countries and Settings	Multi-centre study at two gastroenterology and hepatology clinics in Tehran, Iran
Funding	None reported

Study	Khosravi 2011[505]
Duration of study	2005-2009
Age, gender, ethnicity	Mean age (±SD): 41.36 (±11.18), 86% Male. Ethnicity NR
Patient characteristics	Patients with confirmed NAFLD based on liver biopsy records. Only those liver biopsy specimens were considered which represented fatty liver disease in case of predominantly macrovesicular steatosis or documented steatohepatitis. Negative serologic markers of viral or autoimmune hepatitis. BMI mean (±SD): 27.7 kg/m^2 (±3.8) Upper normal limit (95th percentile) of serum ALT was 35 U/L. ALT activity classified as 'normal' or 'elevated'
Index test	AST/ALT levels
Reference standard	Liver biopsy: no details given
Target condition	Advanced fibrosis
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 0.88** TP 7 FP 28 FN 1 TN 111 Sensitivity 87% Specificity 80.1% Area under the curve 0.836	
General limitations according to QUADAS II: It is unclear whether the index test was interpreted without knowledge of the biopsy outcome. Only patients with a positive NAFLD biopsy were included in the study but retrospective nature of the design leads to concerns around patient selection. No liver biopsy details provided. Unclear how ALT threshold determined.	

Study	Kim 2013[517]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=108)
Countries and Settings	Multi-centre study with 10 participating hospitals in Korea
Funding	Supported by the Research Fund of the Korean Association for the Study of the Liver (KASL)
Duration of study	Jan 2009 – Jul 2011
Age, gender, ethnicity	Mean age (±SD): 38.95 (±13.48), 68% Male. Ethnicity: Korean
Patient characteristics	All patients who underwent liver biopsy for suspected NAFLD based on elevated AST levels for more than 3 months and/or fatty liver detected by ultrasonography. Exclusions: history of significant alcoholic drinking (> 20 g/d), hepatotoxic/herb medication; other causes for liver disease (steatogenic drug abuse, viral, cholestatic, autoimmune, metabolic or hereditary disorder); bariatric surgery within in the previous 5 years Mean BMI (SD): 28.71 (3.77); 86% overweight with BMI >25 kg/m^2. 52% had metabolic syndrome
Index test	Serum samples taken in the morning after a 12 hour overnight fast on the day of liver biopsy and stored at -80°C until just before analysis. Levels of apoptosis-associated CK-18 in sera measured by M30-Apoptosense enzyme-linked immunoassay (ELISA) kit. Ferritin
Reference standard	Liver biopsy using a 16-gauge needle. Specimens were fixed in 10% buffered formalin, embedded in paraffin and stained with hematoxylin and eosin, Masson trichrome, and/or reticulin stain.
Target condition	NASH

Study	Kim 2013[517]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 235.5 U/L** TP 46 FP 14 FN 21 TN 27 Sensitivity 69% Specificity 65% Area under the curve 0.605		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Ferritin: cut-off 160 ng/ml** TP 47 FP 17 FN 20 TN 24 Sensitivity 71% Specificity 58% Area under the curve 0.602
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. All biopsies were reviewed in conference by both hepatopathologists. The hepatopathologists were blinded to all clinical, demographic and laboratory information but unclear if blinded to biopsy outcome when interpreting serum biomarkers. Serum samples for the CK-18 test were obtained on the day of the liver biopsy. Unclear how thresholds determined – not pre-specified.		

Study	Kim 2013[509]
Study type	Retrospective study of MR elastography database
Number of studies (number of participants)	1 (participants with liver biopsy n=142 of 325 with NAFLD and MR elastography data)
Countries and Settings	Single-centre study at an urban clinic, USA
Funding	Supported by the National Institutes of Health grants.
Duration of study	Jan 2007 – Sep 2010
Age, gender, ethnicity	Mean age (±SD): 52.8 (±12.8), 26.8% Male. Ethnicity NR

Study	Kim 2013[509]
Patient characteristics	Adult (>18) patients who underwent liver biopsy within 1 year of MR elastographic examination. Exclusion criteria: evidence of a specific cause for liver disease (such as viral hepatitis B or C, hemochromatosis, autoimmune and cholestatic liver disease, alcoholic liver disease); clinical and/or imaging evidence of hepatic decompensation and portal hypertension such as oesophageal varices; history of liver resection or transplantation; hepatic neoplasm such as HCC or CCA. Mean BMI (±SD): 36.32 (±7.44); 27.5% had diabetes; 45.1% had hypertension
Index test	MR elastography performed according to "established methods as previously published" – 1.5-T whole-bosy imager by using a transmit-receiver coil. Continuous longitudinal waves at 60 Hz were generated using an acoustic pressure waves-transmitted driver device on the anterior chest wall. A two-dimensional gradient-echo MR elastography sequence was performed to acquire axial wave images with the following parameters: repetition time msec/echo time msec, 50/23; continuous sinusoidal vibration, 60 Hz; field of view, 32-42 cm; matrix size, 256 x 64; flip angle, 30°; section thickness, 10mm; four evenly spaced phase offsets; and four pairs of 60-Hz trapezoidal motion-encoding gradients with zeroth and first moment nulling along the through-plane direction. Interpretation of MR elastographic images was performed by staff abdominal radiologists in the Dept of Radiology and liver stiffness measurements obtained at the time of examination ere entered in the database.
Reference standard	Liver biopsy: no details supplied.
Target condition	Advanced fibrosis
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **MR elastograpahy: cut-off 4.15 kPa** TP 39 FP 7 FN 7 TN 89 Sensitivity 85% Specificity 93% Area under the curve 0.945 (0.905-0.982)	

Study	Kim 2013[509]
General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection as patients specified for liver biopsy may differ in a systemic way from those who did not receive it. The hepatopathologists interpreting the liver biopsy specimens were blinded to the MR elastography results but it was unclear if the same was true when interpreting MR images. The liver biopsy was done within 1 year of MR elastographic examination. No details of liver biopsy provided. Thresholds for index test not pre-specified.	

Study	Kruger 2011[543]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=111)
Countries and Settings	Multi-centre study with 3 participating sites in South Africa
Funding	Not reported
Duration of study	Not reported
Age, gender, ethnicity	Mean age (CI): 52 (50-54), 27% Male. Ethnicity: 69% coloured, 25% white, 5% black and 1% Indian
Patient characteristics	Patients with histologically confirmed NAFLD. Exclusions/exclusion criteria: weekly alcohol consumption of > 140 g; other liver diseases. Mean BMI (CI): 35 kg/m^2 (34-36); 43% had type-II diabetes
Index test	APRI calculated using the formula: (AST/upper limit of normal * 100)/platelet count AST/ALT ratio
Reference standard	Liver biopsy: no details provided.
Target condition	Advanced fibrosis

Study	Kruger 2011[543]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence		Results: 2x2 table calculated using author-reported sens, spec and study prevalence
APRI: cut-off 0.98 TP 14 FP 13 FN 5 TN 79 Sensitivity 75% Specificity 86% Area under the curve 0.85		**AST/ALT ratio: cut-off 0.8** TP 11 FP 35 FN 8 TN 57 Sensitivity 58% Specificity 62% Area under the curve 0.61
General limitations according to QUADAS II: it is unclear whether patients were enrolled consecutively. No information is given as to whether the index tests were interpreted without knowledge of the biopsy outcome. No information is given on the time between when the biopsy was done and when the index test was done. Thresholds not pre-specified determined by optimal accuracy. No biopsy method data reported.		

Study	Kumar 2013[547]
Study type	Prospective cohort
Number of studies (number of participants)	1 (patients with NAFLD n=120 of 307 with cirrhosis and healthy controls)
Countries and Settings	Single-centre study at a hepatology department, India
Funding	Not reported
Duration of study	May 2009 – Sep 2011
Age, gender, ethnicity	Mean age (±SD): 39.1 (±12.8), 75% Male. Ethnicity NR
Patient characteristics	All patients attending the clinic during the study period with a histologically confirmed diagnosis. Exclusions/exclusion criteria: alcohol consumption > 20 g/d; liver diseases of other known aetiology; certain

Study	Kumar 2013[547]		
	medications known to induce fatty liver or insulin sensitization (e.g. oestrogens, amiodarone, methotrexate, tamoxifen, pioglitazone, metoformine) Mean BMI (±SD): 26.1 (±3.6); 16.6% had diabetes; 15.8% had hypertension		
Index test	Transient elastography performed using FibroScan (Echosens, France). Examination performed in the right lobe of the liver through intercostal space on patients lying in the dorsal decubitus position with the right arm in maximal abduction. Ten successful acquisitions were performed on each patient using medium probe. Median value of the successful measurements was kept as representative of liver stiffness. TE results were obtained with ten valid measurements with a success rate of at least 60% and an IQR ≤30% was considered reliable. The ratio of IQR/M was calculated in each patient. TE was performed after adequate control of ascites by salt restriction, diuretic, or paracenteisis whenever needed.		
Reference standard	Liver biopsy: An 18-gauge biopsy gun was used, and specimens were fixed in formalin and embedded in paraffin.		
Target condition	Any fibrosis and advanced fibrosis		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **TE: cut-off 4.3 kPa** TP 82 FP 25 FN 6 TN 7 Sensitivity 93% Specificity 22% Area under the curve 0.82 (0.75-0.89)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **TE: cut-off 6.1 kPa** TP 69 FP 10 FN 19 TN 22 Sensitivity 78% Specificity 68% Area under the curve 0.82 (0.75-0.89)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **TE: cut-off 7.3 kPa** TP 51 FP 3 FN 37 TN 29 Sensitivity 58% Specificity 91% Area under the curve 0.82 (0.75-0.89)	

Study	Kumar 2013[547]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **TE: cut-off 7.8 kPa** TP 26 FP 20 FN 1 TN 73 Sensitivity 96% Specificity 78% Area under the curve 0.94 (0.89-0.98)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **TE: cut-off 9.0 kPa** TP 23 FP 11 FN 4 TN 82 Sensitivity 85% Specificity 88% Area under the curve 0.94 (0.89-0.98)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **TE: cut-off 11.2 kPa** TP 19 FP 7 FN 8 TN 86 Sensitivity 71% Specificity 93% Area under the curve 0.94 (0.89-0.98)	
General limitations according to QUADAS II: All patients attending the clinic during the study period were assessed for the presence of NAFLD and NAFLD-related cryptogenic cirrhosis. If NAFLD was suspected on the basis of ultrasonography, the presence of insulin resistance or features of metabolic syndrome, a biopsy was performed to confirm the diagnosis.The liver biopsy was performed the day after the blood tests and FibroScan. The hepatopathologists analysing the specimens were blind to clinical data and the results of the FibroScan but unclear whether the opposite was true. Thresholds for liver stiffness were not predefined.			

Study	Lee 2013[578]
Study type	Retrospective analysis
Number of studies (number of participants)	1 (n=107)
Countries and Settings	Single-centre study at a medical centre, USA
Funding	None reported
Duration of study	2002 – 2006
Age, gender, ethnicity	Mean age (range): 48.9 (40.9-50.0), 38.3% Male. Ethnicity NR

Study	Lee 2013[578]
Patient characteristics	Adults (≥18 years) with a biopsy-confirmed diagnosis of NAFLD/NASH (authors seem to use these terms interchangeably so we cannot be sure that they are all people with definitive NASH) Exclusions/exclusion criteria: history of alcohol abuse; serological evidence of hepatitis virus infection; history of other liver disease (such as haemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis); <18 years old at the time of the biopsy. Mean BMI (range): 35.9 kg/m^2 (29.6-44.7); 32.7% had diabetes; 49% had hypertension; 28.9% had hyperlipidaemia
Index test	BARD score composed of 3 variables: score ranges from 0 to 4 points: AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point
Reference standard	Liver biopsy:no details provided.
Target condition	Advanced fibrosis
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 34 FP 48 FN 0 TN 25 Sensitivity 100% Specificity 35% Area under the curve 0.808 (0.712-0.904)	
General limitations according to QUADAS II: Retrospective nature of the design leads to concerns around patient selection with an unclear population used with respect to NAFLD and NASH or specifically NASH. No information is given about biopsy method or on whether the index test was interpreted without knowledge of the biopsy outcome and how much time passed between the biopsy and the index test. Threshold pre-specified, based on published cut-offs. Patients with missing data not included in ROC analysis but no details of these patients provided.	

Study	Loomba 2014[599]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=117)
Countries and Settings	Single-centre study at the NAFLD Translational Unit, USA
Funding	Not reported
Duration of study	Jan 2011 – Nov 2013
Age, gender, ethnicity	Mean age (±SD): 50.1 (±13.4), 43.6% Male. Ethnicity: 52.1% white, 0.9% black, 17.1% Asian, 27.4% Hispanic, 0.9% multi-racial, 0.9% other, 0.9% refused to disclose
Patient characteristics	Patients with biopsy-proven NAFLD. Liver biopsies were performed for clinical care, and 2D-MRE was done for research. Exclusions/exclusion criteria: <18 years old; regular and excessive alcohol consumption of ≥ 14 drinks (men) or ≥ 7 drinks (women) per week within 2 years preceding recruitment; use of hepatotoxic drugs; use of drugs known to cause hepatic steatosis; clinical/laboratory evidence of secondary NAFLD (due to major nutritional and iatrogenic gastrointestinal disorders, HIV infection), other liver diseases (such as viral hepatitis, Wilson's disease, haemochromatosis, glycogen storage disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis, cholestatic or vascular liver disease) Mean BMI (±SD): 32.4 (±5.0); 34.2% had diabetes
Index test	2D-MRE (magnetic resonance elastography): Continuous vibrations at 60 Hz generated and a 2D gradient-recalled/echo MRE pulse sequence performed while vibrations transmitted, and four non-contiguous axial slices (10mm think, 10mm inter-slice gap) are acquired in a 16 second breath hold through the widest transverse dimension of the liver. Acquisition parameters include repetition time, 50ms; echo time 20.2ms; flip angle 30°, matrix 256x64; field of view 48x48cm; one signal average, receiver bandwidth ±30 kHz and parallel imaging acceleration factor of 2. The mean liver stiffness was calculated by averaging the per-pixel stiffness values across the regions of interest at the four slice locations.
Reference standard	Liver biopsy: no details provided.
Target condition	Any fibrosis and advanced fibrosis

Study	Loomba 2014[599]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **MRE: cut-off 3.02 kPa** TP 41 FP 4 FN 33 TN 39 Sensitivity 55% Specificity 91% Area under the curve 0.838		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **MRE: cut-off 3.64 kPa** TP 19 FP 9 FN 3 TN 86 Sensitivity 86% Specificity 91% Area under the curve 0.924
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. Pathologists analysed the liver biopsies without knowing clinical and radiology data. The median time between the biopsy and the 2D-MRE was 45 days. Thresholds not pre-specified and no information provided on method of biopsy.		

Study	Lupsor 2010[604]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=72)
Countries and Settings	Single-centre study at an urban clinic in Romania
Funding	Romanian Authority for Scientific Research
Duration of study	May 2007 – Sep 2009
Age, gender, ethnicity	Mean age (range): 42 (20-69), 71% Male. Ethnicity NR
Patient characteristics	All patients with NASH visiting the clinic during the study period. Exclusions/exclusion criteria: other acute or chronic liver disease (viral hepatitis, autoimmune hepatitis, primary biliary

Study	Lupsor 2010[604]	
	cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson's disease), history of alcohol consumption of ≥ 30 g/d (men) or ≥ 20 g/d (women), hepatotoxic therapies that might induce steatosis, patients with less than 6 portal spaces on liver biopsy. Mean BMI: 28.71 kg/m^2 (20.96-41.53)	
Index test	Transient elastography performed one day before liver biopsy using FibroScan device with a 5 MHz ultrasound transducer probe. The acquisition was with patients lying in a dorsal decubitus position, with right arm in maximum abduction. The transducer was placed perpendicularly to the intercostal space, in an area free of any large vascular structure. The median value of 10 successful acquisitions was kept to represent liver stiffness.	
Reference standard	Liver biopsy: TruCut technique with a 1.8mm (14G) diameter automatic needle device. The specimens were stained with haematoxylin-eosin, reticulin and Masson trichrome. Median biopsy length was 11 (6-10)mm with a median of 11)7-22) portal spaces.	
Target condition	Any fibrosis and advanced fibrosis	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **TE: cut-off 5.3 kPa** TP 55 FP 8 FN 2 TN 27 Sensitivity 93% Specificity 78% Area under the curve 0.879 (0.779-0.945)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **TE: cut-off 10.4 kPa** TP 5 FP 2 FN 0 TN 65 Sensitivity 100% Specificity 97% Area under the curve 0.978 (0.910-0.997)
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. The pathologist analysing the liver biopsy specimens was blinded to the clinical data but unclear if the opposite was also true. The transient elastogrpahy was performed one day before the liver biopsy. Thresholds were not pre-specifed.		

Study	Mahadeva 2013[619]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=120)
Countries and Settings	University medical centre, Malaysia.
Funding	None reported
Duration of study	August 2009 to June 2010
Age, gender, ethnicity	Mean age (SD): 49.9 (12.3), 53% Male. Ethnicity 43% Malay, 32% Chinese, 24% Indian
Patient characteristics	Adults with liver-biopsy proven NAFLD Exclusions: <18 years, alcohol consumption >20g per day over the past 12 months, patients with specific disease that could lead to steatosis such as hepatitis B or C, drug-induced liver disease or total parenteral nutrition, patients with severe systemis disease and patients with compensated or decompensated liver cirrhosis. 11 were excluded on the basis of unsuccessful LSM measurement. 33% BMI >33 kg/m^2. 47% diabetes, 48% hypertension, 60% dyslipidemia
Index test	Transient elastography performed on same day prior to liver biopsy using FibroScan with M transducer probe. Measures taken on the right hepatic lobe through the intercostal space with the patient lying dorsal decubitus position and the right hand in a maximally abducted position. Ten successful measurements were recorded to obtain median liver stiffness measurement. A success rate of ≥60% and the IQR to median ratio of <30% was regarded as a valid LSM in individual cases. APRI calculated but no details provided.
Reference standard	Liver biopsy: ultrasound guided percutaneous liver biopsy under local anaesthesia using an 18-gauge Temno II semi-automatic biopsy needle. Specimens were fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin. All specimens evaluated by a single pathologist blinded to patients clinical data. Median biopsy length was 13 (IQR 8-15) mm
Target condition	Advanced fibrosis

Study	Mahadeva 2013[619]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut-off 0.5** TP 15 FP 18 FN 14 TN 84 Sensitivity 50% Specificity 82% Area under the curve		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **TE: cut-off 7.10 kPa** TP 20 FP 34 FN 9 TN 68 Sensitivity 70% Specificity 67% Area under the curve 0.77 (0.66-0.87)
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. Thresholds were not pre-specifed. Unclear if TE results interpreted without knowledge of liver biopsy. No details provided on the 11 patients who could not receive a successful LSM.		

Study	Malik 2009[622]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=95)
Countries and Settings	Single-centre study at a liver clinic in Boston, USA
Funding	This study was supported by a number of grants: Liver Institute for Education & Research award, St John Ambulance Air Wing Travelling Fellowship, Foundation for Liver Research Grant.
Duration of study	2003 - 2006
Age, gender, ethnicity	Simple steatosis: mean age (±SD) 49 (±4.9), 64% male, Ethnicity NR NASH: mean age (±SD) 48 (±5.3), 60% male, Ethnicity NR

Study	Malik 2009[622]
Patient characteristics	Inclusion criteria: alcohol consumption < 20 g/d, negative hepatitis serology (viral/autoimmune/metabolic), liver biopsy with histological features of NAFLD 101 patients underwent liver biopsy. Six patients were excluded as an alternative diagnosis was found through the liver biopsy. Simple steatosis: mean BMI (±SD) 30 kg/m^2 (±3.7), 8% had type-II diabetes NASH: mean BMI (±SD) 32 kg/m^2 (±4.7), 38% had type-II diabetes
Index test	CK-18: enzyme linked immunosorbant assay performed with Apoptosense ELISA kit. Sera drawn within 6 months of biopsy.
Reference standard	Liver biopsy: samples were fixed in paraffin, and stained in hematoxylin & eosin and Masson trichrome.
Target condition	NASH
Results: 2x2 table calculated using raw data described in another systematic review[196] as not enough raw data provided in this paper to determine 2x2 table. **CK 18 [M30]: cut-off 300 µ/L** TP 56 FP 13 FN 4 TN 22 Sensitivity 93% Specificity 63% Area under the curve 0.8 (0.76-0.84)	
General limitations according to QUADAS II: Patients were consecutively enrolled in this study. Pathologists analysing the liver biopsy samples were blinded. The clinical, biochemical and histopathological data were reported independently in a blinded fashion. Each patient had serum drawn within 6 months of the liver biopsy. Threshold not pre-specified.	

Study	Manousou 2011[626]
Study type	Retrospective analysis of medical records
Number of studies (number of participants)	1 (n=111)
Countries and Settings	Not reported. This study is a retrospective analysis of medical records in the UK. It is unclear if only one centre was involved in this study.
Funding	Not reported
Duration of study	Not reported
Age, gender, ethnicity	Mean age (SD): 54 (14), 64% Male. Ethnicity NR
Patient characteristics	Patients whose liver biopsies had a database with keywords steatosis and/or steatohepatitis as a pathological diagnosis compatible with NAFLD. Exclusions/exclusion criteria: other types of chronic liver disease (viral hepatitis, autoantibodies, HFE testing, alpha-1 antitrypsin concentrations), lack of clinical data or blood test results, thyroid dysfunction, patients taking thyroxin, alcohol consumption > 21 U (men) or > 14 U (female) per week, patients taking drugs known to cause steatohepatitis (e.g. corticosteroids, methotrexate, oestrogens) Mean BMI: 28.2 kg/m2 (5); 58.3% had diabetes; 26.2% had arterial hypertension; 66% obese. Ferritin defined as abnormal (>340 ng/ml) in 24.5% of the population.
Index test	Serum ferritin
Reference standard	Liver biopsy: no further details provided on method of biopsy
Target condition	NASH

Study	Manousou 2011[626]
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Ferritin: cut-off 240 ng/ml** TP 58 FP 14 FN 6 TN 33 Sensitivity 91% Specificity 70% Area under the curve 0.82 (0.73-0.90)	
General limitations according to QUADAS II: This study reviewed clinical records of consecutive patients with liver biopsies. The retrospective nature of the study design raises concerns about patient selection. No detail provided on biopsy methods. Pathologists reviewing the biopsies were blinded to clinical findings, although unsure if the reverse is also true. Clinical data and blood tests were recorded within 1 month from the liver biopsy. Unclear how thresholds are determined, not pre-specified.	

Study	McPherson 2010[649]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=145)
Countries and Settings	Single-centre study at a specialist clinic in Newcastle, UK
Funding	Not reported
Duration of study	2003 - 2009
Age, gender, ethnicity	Mean age (SD): 51 (12), 61% Male. Ethnicity NR

Study	McPherson 2010[649]
Patient characteristics	Consecutive patients with biopsy-proven NAFLD. Liver biopsies performed as part of the investigation for abnormal liver function test results (elevated ALT, AST or GGT levels) or to stage disease severity in patients with ultrasound evidence of NAFLD and normal liver function test results. Exclusions/exclusion criteria: patients included in a previous study on NAFLD; alcohol consumption of > 30 g/d (men) or > 20 g/d (women); evidence of coexisting liver disease; liver biopsy regarded as inadequate for staging purposes; incomplete data to calculate non-invasive scores (n=65 of 217 original population), previous inclusion in Angulo 2007 (n=7 of 217 original population). Mean BMI (SD): 35 kg/m^2 (5); 87% obese (BMI >29.9); 50.3% had diabetes
Index test	AST/ALT ratio APRI calculated using the formula: {[AST level/upper normal level (33 IU/L)]/[platelet count (10^9/L)]}*100 BARD score composed of 3 variables: score ranges from 0 to 4 points. AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point FIB4-index calculated using the formula: [age(years) * AST level]/[platelet count (10^9/L) * (ALT level)$^{1/2}$] NAFLD fibrosis score: -1.675 + 0.037 – age (years) + 0.094 – BMI + 1.13 * IFG/diabetes (yes = 1, no = 0) + 0.99 * AST/ALT ratio – 0.013 * platelet count (*10^9/L) – 0.66 * albumin (g/dL)
Reference standard	Liver biopsy: percutaneous liver biopsies performed using an 18G BioPince liver biopsy system or a Menghini needle. Mean (SD) biopsy length 22 (8) mm.
Target condition	Advanced fibrosis.

Study	McPherson 2010[649]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut-off 1** TP 6 FP 3 FN 2 TN 9 Sensitivity 27% Specificity 89% Area under the curve 0.67 (0.54-0.8)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 0.8** TP 7 FP 2 FN 1 TN 10 Sensitivity 74% Specificity 78% Area under the curve 0.83(0.74-0.91)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 1** TP 6 FP 2 FN 2 TN 11 Sensitivity 52% Specificity 90% Area under the curve 0.83(0.74-0.91)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 8 FP 2 FN 0 TN 19 Sensitivity 89% Specificity 44% Area under the curve 0.77(0.68-0.87)
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 1.30** TP 6 FP 3 FN 2 TN 9 Sensitivity 85% Specificity 65% Area under the curve 0.86(0.78-0.94)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 3.25** TP 7 FP 2 FN 1 TN 10 Sensitivity 26% Specificity 98% Area under the curve 0.86(0.78-0.94)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off -1.455** TP 6 FP 2 FN 2 TN 11 Sensitivity 78% Specificity 58% Area under the curve 0.81(0.71-0.91)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off 0.676** TP 8 FP 2 FN 0 TN 19 Sensitivity 33% Specificity 98% Area under the curve 0.81(0.71-0.91)
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. It is unclear whether the biopsy was interpreted without knowledge of the index test results or vice versa. Blood test results from the time of the liver biopsy or within 3 months were recorded. Thresholds pre-specified, based on previously published cut-offs. Not all patients included in analysis – excluded if incomplete index test data. No information provided on			

Study	McPherson 2010[649]
those excluded on this basis.	

Study	Neuschwander-Tetri 2010[695]
Study type	Retrospective database analysis
Number of studies (number of participants)	2 (NASH CRN study n=1019; PIVENS study n=247; patients with liver biopsy within 6 months of either study n=698; (used for diagnostic accuracy calculation)
Countries and Settings	Multi-centre study with 9 participating medical centres, USA
Funding	This study was supported by a number of grants from the National Institute of Health (NIH)
Duration of study	Enrolment Oct 2004 – Feb 2008, follow-up till Sep 2009
Age, gender, ethnicity	Mean age: 49, 39% Male. Ethnicity: 81% white, 14% Hispanic
Patient characteristics	Histological diagnosis of NAFLD. Exclusion criteria (NASH CRN study): alcoholic liver disease, alcohol consumption of > 20 g/d (men) or > 10 g/d (women) during the two years before entry, other forms of liver disease, history of total parenteral nutrition, biliopancreatic diversion, bariatric surgery, short bowel syndrome, suspected or confirmed hepatocellular carcinoma, HIV positive, conditions that were likely to interfere with study follow-up, inability to provide informed consent Exclusion criteria (PIVENS study): < 18 years old, alcohol consumption of > 30 g/d (men) or > 20 g/d (women) at the time of study or for a period of more than 3 consecutive months in the 5 years prior to screening, any form of chronic liver disease, use of medications thought to cause or affect NAFLD, use of non-stable doses of lipid lowering medications, ALT levels > 300 U/L, serum creatinine levels ≥ 2.0 mg/dL, pregnant women, unwilling to use effective birth control or nursing Mean BMI: 34 kg/m^2; 44% had hypertension, 22% had type-II diabetes, 62% had metabolic syndrome
Index test	ALT levels. Different cut-offs examined for upper reference range: • Conservative cut-off of 19 U/L for women and 30 U/L for men

Study	Neuschwander-Tetri 2010[695]	
	• Setting upper limit arbitrarily at 40 U/L	
Reference standard	Liver biopsy: all biopsy specimens were formalin fixed and paraffin embedded. Hematoxylin and Eosin, Masson's trichrome and Perls' iron stains were prepared by a central laboratory and reviewed centrally by the NASH CRN Pathology Committee. 14% of biopsies were less than 10 mm in length.	
Target condition	NASH	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: conservative cut-off 19 U/L for women and 30 U/L for men** TP 400 FP 268 FN 4 TN 23 Sensitivity 99% Specificity 8% Area under the curve NR		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: conservative cut-off 40 U/L** TP 347 FP 198 FN 57 TN 93 Sensitivity 86% Specificity 32% Area under the curve NR
General limitations according to QUADAS II: it is unclear whether patients were enrolled consecutively to the two studies. All liver biopsy specimens were reviewed centrally by a committee of nine hepatologists, who were blinded to all clinical and identifying data. Unclear about opposite situation. It is unclear in the paper if the diagnostic accuracy is determined based on the population who had liver biopsy within 6 months or the population who had liver biopsy performed at any time. Thresholds for ALT levels pre-specified.		

Study	Nobili 2008[702]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=67)
Countries and Settings	Single-centre study at a children's hospital in Rome, Italy
Funding	Not reported
Duration of study	15 Jul 2007 – 15 Jan 2008
Age, gender, ethnicity	Mean age (range): 13.6 (4-17), 62% Male. Ethnicity NR
Patient characteristics	Children and adolescents with persistent or intermittent elevation of serum aminotransferases associated with diffusely hyperechogenic liver tissue at US examination, and hyperinsulinism Exclusions/exclusion criteria: cardiopulmonary disease, chronic renal failure, recent-active infections, chronic inflammatory drugs, abnormal INR, autoimmune diseases, use of anti-inflammatory drugs, platelet count < $60*10^9$/L, secondary causes of steatosis, alcohol abuse (≥ 140 g/week), total parenteral nutrition, rapid weight loss, endocrinological diseases, inborn disorders, inflammatory bowel disease, use of drugs known to cause steatosis F0 (n=11): mean BMI (±SD) 24 kg/m^2 (±6); 5% were obese; 9% were overweight F1 (n=27): mean BMI (±SD) 26 kg/m^2 (±4); 14% were obese; 21% were overweight F2 (n=7): mean BMI (±SD) 27 kg/m^2 (±6); 2% were obese; 4% were overweight F3-4 (n=5): mean BMI (±SD) 26 kg/m^2 (6±); 3% were obese; 3% were overweight
Index test	Transient elastography performed using the FibroScan (provided by Axsan, Milan) consisting of 3.5 –MHz ultrasound transducer probe. Patient lying in dorsal decubitus with the right up at maximal abduction TE done on an adequate section of liver tissue free of large vascular structures and gallbladder in the intercostal space on the right lobe. Stiffness was measured on a cylinder of hepatic tissue 1cm in diameter and 2-4cm in length. Representative measurements with the median value of 10 successful acquisitions with a success rate of at least 60% and with an IQR less than 30% were considered.
Reference standard	Liver biopsy: performed using an 18G needle under general anaesthesia and ultrasound guidance. Only samples with a length of ≥15 mm and including at least 10-11 complete portal tracts were considered adequate for the purpose of the

Study	Nobili 2008[702]	
	study. 5 micrometre thick samples were stained with hematoxylin-eosin, Masson trichrome, Van Gieson, periodic acid Schiff stain after diastase digestion, and Prussian blue stain.	
Target condition	Any fibrosis and advanced fibrosis	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **TE: cut-off 5.1 kPa** TP 38 FP 1 FN 1 TN 10 Sensitivity 97% Specificity 91% Area under the curve 0.97 (0.90-0.99)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **TE: cut-off 10.2 kPa** TP 5 FP 0 FN 0 TN 45 Sensitivity 100% Specificity 100% Area under the curve 1 (0.94-1)
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. The histopathologist analysing the liver biopsy specimens was blinded to the clinical and laboratory data, and the investigators performing the TE were blinded to the clinical and histopathological data. All patients underwent TE within 6 months of the liver biopsy.		

Study	Nobili 2009[701]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=112)
Countries and Settings	Single-centre study at a children's hospital in Rome, Italy

Study	Nobili 2009[701]
Funding	One author is employed by iQur Limited, another author holds stock in iQur Limited
Duration of study	Jun 2004 – Nov 2006
Age, gender, ethnicity	Mean age (range): 14.1 (3-17), 56% Male. Ethnicity NR
Patient characteristics	Children and young people with diagnosed NAFLD, who have been referred to the specialist clinic due to serum aminotransferases either persistently or intermittently elevated (at least two abnormal determinations within 6 months prior to enrolment), associated with diffusely hyperechogenic liver tissue (bright liver) at ultrasound examination, and hyperinsulinism. Exclusions/exclusion criteria: cardiopulmonary disease, chronic renal failure, recent-active infections, chronic inflammatory drugs, abnormal INR, autoimmune diseases, use of anti-inflammatory drugs, platelet count < $60*10^9$/L, secondary causes of steatosis, alcohol abuse (≥ 140 g/week), total parenteral nutrition, rapid weight loss, endocrinological diseases, inborn disorders, inflammatory bowel disease, use of drugs known to cause steatosis F0 (n=37): mean BMI (±SD) 25.34 kg/m^2 (±3.93); 35.1% were obese; 64.8% were overweight F1a (n=8): mean BMI (±SD) 24.94 kg/m^2 (±3.58); 37.5% were obese; 62.5% were overweight F1b (n=6): mean BMI (±SD) 24.48 kg/m^2 (±4.78); 50% were obese; 50% were overweight F1c (n=44): mean BMI (±SD) 25.36 kg/m^2 (±4.37); 45.4% were obese; 54.5% were overweight F2 (n=9): mean BMI (±SD) 26.08 kg/m^2 (±2.98); 22.2% were obese; 77.7% were overweight F3-4 (n=8): mean BMI (±SD) 26.61 kg/m^2 (±0.24); 62.5% were obese; 37.5% were overweight
Index test	ELF test. Algorithm: -7.412 + [ln(HA)*0.681) + (ln(P3NP)*0.775) + (ln(TIMP1)*0.494] + 10
Reference standard	Liver biopsy: performed using an 18G needle under general anaesthesia and ultrasound guidance. Only samples with a length of ≥15 mm and including at least 10-11 complete portal tracts were considered adequate for the purpose of the study. 5 micrometre thick samples were stained with hematoxylin-eosin, Masson trichrome, Van Gieson, periodic acid Schiff stain after diastase digestion, and Prussian blue stain.
Target condition	Any fibrosis and advanced fibrosis

Study	Nobili 2009[701]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **ELF: cut-off 9.28** TP 66 FP 7 FN 9 TN 30 Sensitivity 88% Specificity 81% Area under the curve 0.92 (0.86-0.97)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **ELF: cut-off 10.51** TP 8 FP 2 FN 0 TN 102 Sensitivity 100% Specificity 98% Area under the curve 0.99 (0.97-1.00)
General limitations according to QUADAS II: Patients were recruited consecutively. Biopsies were reviewed by a single liver pathologist, who was blinded to the ELF test results. It is unclear if the investigator analysing the ELF test was blinded to the biopsy results or clinical data. The blood tests for the ELF test were done on the same day as the liver biopsy. Thresholds not pre-specified.		

Study	Palmeri 2011[737]
Study type	Retrospective/prospective design (the design of the study is unclear)
Number of studies (number of participants)	1 (n=135)
Countries and Settings	Single-centre study at a university medical centre, USA
Funding	Supported by NIH grant and NIH/NIDDK Mentored Career Development Award
Duration of study	March 2008 – March 2010
Age, gender, ethnicity	Mean age NR, 38% Male. Ethnicity NR

Study	Palmeri 2011[737]
Patient characteristics	Adults with histologically proven NAFLD Exclusions/exclusion criteria: <18 years old, liver histology data unavailable, alcohol consumption of ≥14 drinks (men) or ≥7 drinks (women) per week, other coexisting causes of chronic liver disease as determined by hepatologist. n=38 of original 172 excluded due to unsuccessful shear stiffness reconstruction using the RANSAC algorithm. BMI <18 (n=1), 18-23 (n=8), 23-30 (n=39), 30-40 (n=68), >40 (n=19)
Index test	Acoustic radiation force impulse (ARFI): shear wave data aqcuistion and processing using a customised Siemens SONOLINE Antares scanner and a CH41 transducer. Five different people performed the imaging (inter-rater variability not analysed. All patients were imaged within minutes of biopsy. Shear stiffness was characterised in three different locations in the liver: superior intercostal, inferior intercostal and lateral subcostal. Three replicate shear stiffness data acquisitions were performed in each location for a total of nine per patient.
Reference standard	Liver biopsy: liver biopsy specimens stained with hematoxylin-eosin and Masson trichrome stains
Target condition	Advanced fibrosis
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ARFI: cut-off 4.24 kPa** TP 36 FP 10 FN 4 TN 85 Sensitivity 90% Specificity 90% Area under the curve 0.90	
General limitations according to QUADAS II: it is unclear whether patients were enrolled consecutively to this study. It is unclear whether the study was based on analysis of records or a prospective design. It is unclear whether the index test was interpreted without knowledge of the liver biopsy outcome. It is also unclear how much time passed between the liver biopsy and the index test. Threshold not pre-specified.	

Study	Papatheodoridis 2010[740]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=58 with NAFLD of a total including 134 chronic hepatitis C)
Countries and Settings	Greece; unclear how many centres.
Funding	None reported
Duration of study	January 2004 – March 2006
Age, gender, ethnicity	Mean age (SD): NASH 48 (13), non-NASH 46 (16). Gender: NASH 53% male, non-NASH 57% male. Ethnicity NR
Patient characteristics	All patients admitted for liver biopsy who had been followed for six months at liver outpatient clinics before admission. Excluded: Patients with malignancy or any type of antiviral therapy in the past or any type of immunomodulatory therapy within the last 12 months as well as those with an inadequate biopsy specimen were excluded. Patients with a positive hepatitis B surface antigen or detectable anti-bodies against HIV were also excluded. No patient had decompensated liver disease. Mean BMI: NASH 30 (5) kg/m^2, non-NASH 27 (4) kg/m^2, *p*=0.02
Index test	Commercially available assays were used for all serological determinations. The levels of caspase-generated CK 18 fragments were blindly measured in serum samples stored at -80° on the day of liver biopsy using an M30-Apoptosense ELISA assay. Determinations for the first 40 samples were performed in duplication under blinded code conditions. The mean inter-assay variation was 1.8% (including first 40 HCV and first 40 healthy control samples)
Reference standard	Liver biopsy: All biopsies had an adequate specimen length ≥1.5 cm. 2 NAFLD biopsies were excluded because of an inadequate liver specimen as it was predefined if no portal tracts were identified or the specimen size itself made it impossible to make a proper evaluation. All liver biopsies were studied blindly by a single liver histopathologist.
Target condition	NASH

Study	Palmeri 2011[737]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK-18 [M30]: cut-off 225 U/L** TP 21 FP 5 FN 9 TN 23 Sensitivity 70% Specificity 82% Area under the curve 0.87 (0.79-0.96)	Results: 2x2 table calculated using using author-reported sens, spec and study prevalence **CK-18 [M30]: cut-off 250 U/L** TP 18 FP 2 FN 12 TN 26 Sensitivity 60% Specificity 93% Area under the curve 0.87 (0.79-0.96)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK-18 [M30]: cut-off 300 U/L** TP 16 FP 0 FN 14 TN 28 Sensitivity 53% Specificity 100% Area under the curve 0.87 (0.79-0.96)	
General limitations according to QUADAS II: Consecutively included patients. Unclear how thresholds determined. CK 18 interpreted without knowledge of biopsy results (blinded) and performed on the same day as biopsy. Thresholds not pre-specified.			

Study	Pathik 2015 [752]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=110)
Countries and Settings	Single centre outpatient department for dyspepsia, India
Funding	None reported.
Duration of study	December 2011 to December 2012
Age, gender, ethnicity	Mean age (SD): 42.37 (3.2); Sex F:M 2.3:1; Ethnicity: NR
Patient characteristics	Adults (18 to 80 years) attending the outpatient department of tertiary care centre (non-referred patients) for dyspepsia and who were diagnosed with fatty liver on ultrasound (hyper-echoic liver where the echo-texture of the liver was brighter than the kidney, and had blurred vascular margins and deep attenuation of ultrasound signal). Of

Study	Pathik 2015 [752]
	these, patient with any one of the following were selected for liver biopsy: diabetes (fasting blood sugar >126 g/dL); metabolic syndrome (diagnosed on the basis of NCEP-ATPIII criteria); BMI >30 kg/m^2; serum AST/alanine aminotransferase (ALT) greater than the upper limit of normal (40IU/mL); and hyperthyroidism (serum thyroid stimulating hormone >5.5 IU/mL). Exclusion criteria: history of alcohol intake greater than 20 g per day (during previous 5 years); hepatits B surface antigen reactive; presence of antibody against hepatitis C; HIV; active hepatitis; biliary obstruction on ultrasonography; cirrhosis diagnosed at any time in the past; tuberculosis; malabsorption; chronic drug use; pregnancy; and those with any cardio-respiratory comorbidities. Alpha-1 antitrypsin deficiency and hemochromatosis are rarely seen in Indian patients and thus were not investigated. 8 people denied consent of 118 that were high-risk and indicated for liver biopsy.
Index test	Fibroscan (M probe, Echosens, Paris) carried out by an experienced examiner in all patients (with at least 6 h of fasting) in left lateral position and the median liver stiffness of the 10 successful measurements fulfilling the criteria (success rate of greater than 60% and interquartile range/median ratio of <30%) were noted in kPa. APRI AST/ALT ratio NAFLD fibrosis score: -1.675+0.037 x age (years) + 0.094 x BMI + 1.13 x impaired fasting glucose/diabetes (yes=1, no=0) + 0.99 x AST/ALT ratio – 0.013 x platelet (X10^9/L) -0.66 x albumin.
Reference standard	Liver biopsy with a 16 gauge needle and a specimen of minimum 2cm length was obtained. All liver biopsies were assessed by a senior histopathologist and were graded according to Brunt criteria.
Target condition	Advanced fibrosis

Study	Pathik 2015 [752]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Fibroscan [M probe]: cut-off 12 kPa** TP 34 FP 14 FN 4 TN 58 Sensitivity 90% Specificity 80% PPV 72% NPV 93% Area under the curve 0.91	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut off 1.0** TP 27 FP 14 FN 11 TN 58 Sensitivity 70% Specificity 80% PPV 60% NPV 84% Area under the curve NR	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut off 1.6** TP 30 FP 0 FN 8 TN 72 Sensitivity 80% Specificity 100% PPV 100% NPV 92% Area under the curve NR
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut off -1.455** TP 31 FP 0 FN 7 TN 72 Sensitivity 100% Specificity 69% PPV 62% NPV 100% Area under the curve NR	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off 0.676** TP 38 FP 22 FN 0 TN 50 Sensitivity 82% Specificity 100% PPV 100% NPV 92% Area under the curve NR	

Study	Pathik 2015 [752]
General limitations according to QUADAS II: Index test threshold pre-defined. Unclear blinding between those reading index test and reference standard. Unclear timing between reference test and index tests. Unclear if recruitment was consecutive.	

Study	Perez-Gutierrez 2013[759]
Study type	Retrospective analysis of patient information
Number of studies (number of participants)	1 (n=228)
Countries and Settings	Mexico and Chile, multi-centre Department of Pathology and Department of Gastroenterology.
Funding	Partially supported by medica Sur & Clinic and Foundation and by grants from the Chilean National Fund for Research in Science and Technology and the National Council for Scientific and Technological Research.
Duration of study	Between January 2005 and December 2010 (Mexico) Between January 2007 and November 2011 (Chile)
Age, gender, ethnicity	Mean age (SD): 48.6 (12.7). Male 49%. Ethnicity NR
Patient characteristics	Patients with histopathological diagnosis of NAFLD according to Brunt's criteria with complete data from liver function tests and a blood count within 3 months of the date of the liver biopsy and anthropometric measurements recorded in the electronic file. Excluded patients who exhibited histopathological evidence or clinical data suggesting the presence of other associated liver diseases (primary biliary cirrhosis, chronic infection with hepatitis B or C, autoimmune hepatitis, sclerosing cholangitis, or overlapping syndrome) or evidence of alcohol intake of more than three drinks of any alcoholic beverage per week. 15 excluded of original 243 due to lack of clinical, laboratory or other secondary diagnostic results. 23.6% Obese.
Index test	APRI = {AST (IU/l)/[upper normal value of 41 (IU/l)]}/platelet count (x10^9/l) x 100 AST/ALT ratio BARD = sum obtained from the three variables of BMI > 28 = 1 point; AST/ALT ratio >0.8 = 2 points; Diabetes = 1 point FIB4= age x AST (IU/l)/platelet count (x10^9/l) x √ALT (IU/l) NAFLD fibrosis score = 1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x abnormal fasting glucose level or

Study	Perez-Gutierrez 2013[759]		
	diabetes (yes =1; no=0) + 0.99 x AST/ALT ratio – 0.013 x number of platelets (x10^9/l) – 0.99 x albumin concentration (g/dL)		
Reference standard	Liver biopsy: samples stained with hematoxylin and eosin, and Masson's trichome stain. Biopsies reviewed by two expert pathologists in each centre, who reached consensus on the results.		
Target condition	Advanced fibrosis.		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut-off 1** TP 10 FP 28 FN 17 TN 173 Sensitivity 37% Specificity 86% Area under the curve 0.66 (0.55-0.77)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 1** TP 18 FP 76 FN 9 TN 125 Sensitivity 66% Specificity 62% Area under the curve 0.67 (0.57-0.77)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 21 FP 115 FN 6 TN 86 Sensitivity 76% Specificity 43% Area under the curve 0.65 (0.52-0.77)	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 3.25** TP 15 FP 22 FN 12 TN 179 Sensitivity 56% Specificity 89%	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off 0.676** TP 14 FP 26 FN 13 TN 175 Sensitivity 53% Specificity 87%		

Study	Perez-Gutierrez 2013[759]	
Area under the curve 0.74 (0.65-0.84)		Area under the curve 0.72 (0.60-0.83)
General limitations according to QUADAS II: Unclear if patients were enrolled consecutively given retrospective nature of the study design. Unclear if all aspects of index test scores were taken on the same day as liver biopsy. Thresholds for index test scores were pre-specified. Unclear whether those interpreting index tests were blinded to the biopsy results.		

Study	Petta 2011[762]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=146)
Countries and Settings	Single-centre study at a university hospital in Italy
Funding	Not reported
Duration of study	Jan 2006 – Dec 2010
Age, gender, ethnicity	Mean age (SD): 44.1 (13.2), 71% Male. Ethnicity NR
Patient characteristics	Diagnosis of NAFLD based on chronically elevated ALT for at least 6 months, alcohol consumption <20 g/day in the last year (≥5% of hepatocytes) at histology with/without necroinflammation and/or fibrosis. Exclusions/exclusion criteria: advanced cirrhosis (Child-Turcotte-Pugh B and C), hepatocellular carcinoma, other causes of liver disease or mixed aetiologies (alcohol abuse, hepatitis C, hepatitis B, autoimmune liver disease, Wilson's disease, haemochromatosis or alpha-1 antitrypsin deficiency), HIV infection, previous treatment with immunosuppressive drugs, active intravenous drug addiction, use of cannabis. 23 of original 196 patients were excluded as there was a failure to obtain 10 valid LSM acquisitions due to obesity. Mean BMI (SD): 29.1 kg/m^2 (4.1); 86% had diabetes; 82% had hypertension
Index test	Transient elastography performed using the FibroScan medical device using the M probe to measure liver stiffness (LSM). LSM was performed on the same day of liver biopsy by a single staff physician. The median value of 10 successful acquisitions was maintained as representative of LSM. 10 successful acquisitions with a success rate of at least 50% and with an IQR lower than 20% were considered as representative measurements.
Reference standard	Liver biopsy: a minimum length of 15 mm of biopsy specimen or the presence of at least 10 complete portal tracts was required. Mean length of liver fragments was 17 mm (range 15-31), and the mean number of complete portal tracts in

Study	Petta 2011[762]
	the specimens was 12.
Target condition	Any fibrosis
Results: 2x2 table calculated using author-reported raw data **TE: cut-off 8.75 kPa** TP 25 FP 25 FN 8 TN 88 Sensitivity 76% Specificity 78% Area under the curve 0.870	
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. Pathologists interpreting the biopsy specimens were blinded to clinical and demographical data, but unclear whether the opposite was true for the index test. The TE was performed on the same day of the liver biopsy. Threshold not pre-specified.	

Study	Qureshi 2008[795]
Study type	Retrospective analysis of medical records
Number of studies (number of participants)	1 (n=331)
Countries and Settings	USA, single centre.
Funding	Not reported
Duration of study	January 2002 – February 2007
Age, gender, ethnicity	Mean age (SD): 40.5 (8.5), 17% Male. Ethnicity 86% non-Hispanic whites/other

Study	Qureshi 2008[795]	
Patient characteristics	All patients with clinically severe obesity who underwent laparoscopic Roux-en-Y Gastric Bypass surgery identified as NALFD by routine biopsy. Exclusions: Patients with <5% steatosis on biopsy (70 of original 401 people). Mean BMI (SD): 48.4 kg/m^2 (7.2); 35% had diabetes	
Index test	NAFLD fibrosis score: -1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x IFG/diabetes (yes=1, no=0) + 0.99 x AST/ALT ratio – 0.013 x platelet (x109/L) – 0.66 x albumin (g/dL).	
Reference standard	Liver biopsies performed on the left lobe of the liver at the beginning of the operation using a Tru-cut needle. The liver biopsy was interpreted by a single pathologist blinded to all clinical data. Mean biopsy length 26.9 (1.1) mm.	
Target condition	Any fibrosis and advanced fibrosis	
Results: 2x2 table calculated using author-reported raw data **Any fibrosis** **NAFLD fibrosis score: cut-off -1.455** TP 161 FP 60 FN 49 TN 110 Sensitivity 77% Specificity 50% Area under the curve NR	Results: 2x2 table calculated using author-reported raw data **Any fibrosis** **NAFLD fibrosis score: cut-off 0.676** TP 59 FP 8 FN 151 TN 113 Sensitivity 28% Specificity 93% Area under the curve NR	

Study	Qureshi 2008[795]	
Results: 2x2 table calculated using author-reported raw data **Advanced fibrosis** **NAFLD fibrosis score: cut-off -1.455** TP 43 FP 178 FN 2 TN 108 Sensitivity 96% Specificity 38% Area under the curve NR		Results: 2x2 table calculated using author-reported raw data **Advanced fibrosis** **NAFLD fibrosis score: cut-off 0.676** TP 22 FP 45 FN 23 TN 241 Sensitivity 49% Specificity 84% Area under the curve NR
General limitations according to QUADAS II: Patients were enrolled consecutively to this study, however retrospective nature of the study design leads to concerns about patient selection (including unclear exclusion criteria). Unclear whether the index test was interpreted without knowledge of reference standard result. Also unclear interval between biopsy and index tests. Thresholds pre-specified.		

Study	Raszeja-Wyszomirska 2010[802]
Study type	Retrospective analysis
Number of studies (number of participants)	1 (n=103)
Countries and Settings	Poland, multi-centre study with two participating liver centres.
Funding	This study was supported by a grant from the State Committee for Scientific Research
Duration of study	Not reported
Age, gender, ethnicity	Mean age (SD): 48 (12), 65% Male. Ethnicity Caucasian
Patient characteristics	Patients with biopsy-proven fatty liver (> 5% of steatotic hepatocytes) referred due to elevated liver enzymes and/or hyerintense echo on abdominal ultrasound and negative history of alcohol intake.

Study	Raszeja-Wyszomirska 2010[802]
	Exclusions/exclusion criteria: alcohol consumption > 20g/d, positive viral hepatitis B or C results Mean BMI (SD): 29.6 (3.84); 38.1% were overweight
Index test	BARD score composed of 3 variables: score ranges from 0 to 4 points for AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point
Reference standard	Liver biopsy: no details supplied.
Target condition	Advanced fibrosis
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 13 FP 24 FN 2 TN 64 Sensitivity 87% Specificity 73% Area under the curve 0.821	
General limitations according to QUADAS II: Retrospective nature of the study design leads to concerns about patient selection. No information is supplied about the method of liver biopsy. It is unclear whether the index test was interpreted without knowledge of the biopsy outcome, and how much time passed between the biopsy and the index test. Threshold pre-specified.	

Study	Ratziu 2006[806]
Study type	Prospective cohort
Number of studies (number of participants)	2 (CYTOL study n=97; reference n=170)
Countries and Settings	Reference group: single-centre study at a hepato-gastroenterology department in France CYTOL study: multi-centre study

Study	Ratziu 2006[806]
Funding	Grants from the Association pour la Recherche sur le Cancer and the Association de Recherche sur les Maladies Virales Hepatiques
Duration of study	Reference group: Jan 2001 – Dec 2004 CYTOL study: Feb 2002 – Aug 2004
Age, gender, ethnicity	Reference group: mean age 52.8, 58% male CYTOL study: mean age 48.5, 59% male
Patient characteristics	Reference group: NAFLD patients hospitalised having undergone liver biopsy. Abnormal serum transaminases or GGT, or steatosis at sonography, or one feature of metabolic syndrome – fasting glucose >6.1 mmol/l or a previous diagnosis of diabetes, BMI ≥27 or waist circumference >102cm (men) or 88cm (women), blood pressure >130/85 or pharamcologially treated, triglyceride-levels >150 mg/dl or current use of fibrates, HDL-cholesterol <40 mg/dl (men) or 50 (women). CYTOL group: Patients with chronic abnormal ALT or GGT values without heavy alcohol consumption, without markers for other miscellaneous liver diseases. Exclusions (reference group): alcohol consumption of ≥ 50g/d (men) or ≥30g/d (women) of pure ethanol during the preceding year, concomitant liver disease, HIV antibodies and immunosuppression, interval greater than 3 months between serum sample and liver biopsy Exclusions (CYTOL study): heavy alcohol consumption, HCV antibodies, HBV antigen, autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency. Reference group: 36% had diabetes, 31% had hypertension, 60% had a BMI > 27 CYTOL study: 32% had diabetes, 16% had hypertension, 44% had a BMI > 27
Index test	FibroTest (age, gender, bilirubin, GGT, apolipoprotein A1, haptoglobin, α-2 macroglobulin)
Reference standard	Liver biopsy: specimens were fixed, paraffin-embedded and stained with at least hematoxylin-eosin-safran, iron staining and Masson's trichrome or picrosirius red for collagen.
Target condition	Advanced fibrosis

Study	Ratziu 2006[806]	
Results: 2x2 table calculated using author-reported raw data **Study 1 (reference group)** **Fibrotest: cut-off 0.30** TP 19 FP 43 FN 1 TN 107 Sensitivity 95% Specificity 71% Area under the curve 0.92 (0.83-0.96)		Results: 2x2 table calculated using author-reported raw data **Study 1 (reference group)** **Fibrotest: cut-off 0.70** TP 5 FP 4 FN 15 TN 146 Sensitivity 25% Specificity 97% Area under the curve 0.92 (0.83-0.96)
Results: 2x2 table calculated using author-reported raw data **Study 2 (CYTOL group)** **Fibrotest: cut-off 0.30** TP 14 FP 25 FN 2 TN 56 Sensitivity 88% Specificity 69% Area under the curve 0.81 (0.64-0.91)		Results: 2x2 table calculated using author-reported raw data **Study 2 (CYTOL group)** **Fibrotest: cut-off 0.70** TP 4 FP 1 FN 8 TN 80 Sensitivity 25% Specificity 99% Area under the curve 0.81 (0.64-0.91)
General limitations according to QUADAS II: It is not clear whether patients were enrolled consecutively. The pathologist interpreting the liver biopsy specimens was blinded to patient characteristics. The interval between the liver biopsy and the serum sample was less than 3 months for the reference group. No information is given for the CYTOL study. Unclear if thresholds were pre-specified.		

Study	Ruffillo 2011[818]	
Study type	Retrospective analysis	
Number of studies (number of participants)	1 (n=138)	
Countries and Settings	Single-centre study at a liver unit of an urban hospital, Argentina.	
Funding	None declared	
Duration of study	Not reported	
Age, gender, ethnicity	Mean age (interquartile range): 49 (38-57), 49% Male. Ethnicity NR	
Patient characteristics	Most patients had been referred to the liver unit for presenting abnormal liver enzymes or a diffusely hyperechogenic liver abdominal ultrasound Exclusions: alcohol consumption of ≥ 140/week, other aetiologies of chronic liver disease, less than 5% of hepatocytes showing macrovesicular steatosis in liver biopsy Mean BMI (interquartile range): 30.3 kg/m^2 (27.8-34.5); 23% had diabetes; 57% were obese	
Index test	BARD score composed of 3 variables: score ranges from 0 to 4 points: AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point NAFLD fibrosis score: -1.675 + 0.037 – age (years) + 0.094 – BMI + 1.13 * IFG/diabetes (yes = 1, no = 0) + 0.99 * AST/ALT ratio – 0.013 * platelet count (*10^9/L) – 0.66 * albumin (g/dL)	
Reference standard	Liver biopsy: all samples were obtained using the Menghini method by the percutaneous route, assuring a length of at least 25mm. Specimens were stained with hematoxylin-eosin, silver reticulin, Masson trichrome, and occasionally with Perls' Prussian blue and diastase-resistant periodic acid-Schiff.	
Target condition	Adavanced fibrosis	
Results: 2x2 table calculated using author-reported raw data **BARD: cut-off 2** TP 19 FP 23	Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off -1.455** TP 20 FP 27	Results: 2x2 table calculated using author-reported raw data **NAFLD fibrosis score: cut-off 0.676** TP 5 FP 0

Study	Ruffillo 2011[818]		
FN 18 TN 78 Sensitivity 51% Specificity 77% Area under the curve 0.67 (0.56-0.77)	FN 17 TN 74 Sensitivity 54% Specificity 72% Area under the curve 0.68 (0.57-0.78)	FN 32 TN 101 Sensitivity 13% Specificity 100% Area under the curve 0.68 (0.57-0.78)	
General limitations according to QUADAS II: Patients were enrolled consecutively. It is unclear if the pathologist analysing the biopsy specimens was blinded to the index test and clinical data. It is also unclear if the index tests were interpreted without knowledge of the biopsy outcome. Laboratory analysis was done within two weeks before the liver biopsy. Thresholds pre-specified from previously published cut-offs.			

Study	Shah 2009[861]
Study type	Retrospective analysis
Number of studies (number of participants)	1 (n=541)
Countries and Settings	USA. Data is taken from the NIH NASH Clinical Research Network (CRN), which consists of three databases. Two of the three databases were used for this study.
Funding	Supported by grants from the National Institute of Health (NIH)
Duration of study	Not reported
Age, gender, ethnicity	Mean age (SD): 48 (12), 40% Male. Ethnicity: 74% Caucasian
Patient characteristics	People with histologically proven NAFLD enrolled in a 1)natural history database or 2) a randomised clinical trial of pioglitazone or vitamin E versus placebo (PIVENS) in adults. Exclusions/exclusion criteria: incomplete datasets, paediatric patients, other causes of liver disease (hepatitis B/C, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, primary biliary cirrhosis), in patients with a positive antinuclear antibody test the presence of piecemeal necrosis or other histologic features of autoimmune hepatitis as well as hypergammaglobulinaemia, alcohol consumption of ≥ 30 g/d (men) or ≥ 20 g/d (women) over the previous 5 years Mean BMI (SD): 34 kg/m^2 (6.3); 44% had hypertension; 19% had type-II diabetes

Study	**Shah 2009[861]**	
Index test	Baseline data obtained from records at time closest to liver biopsy. FIB4-index calculated using the formula: [age(years) * AST level]/[platelet count (10^9/L) * (ALT level)$^{1/2}$] BARD score composed of 3 variables: score ranges from 0 to 4 points: AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point	
Reference standard	Liver biopsy: no specific method described	
Target condition	Advanced fibrosis	
Results: 2x2 table calculated using author-reported raw data **BARD: cut-off 2** TP 91 FP 163 FN 34 TN 253 Sensitivity 73% Specificity 61% Area under the curve 0.70 (0.64-0.75)	Results: 2x2 table calculated using author-reported raw data **FIB4: cut-off 1.30** TP 92 FP 122 FN 33 TN 294 Sensitivity 74% Specificity 71% Area under the curve 0.802 (0.758-0.847)	Results: 2x2 table calculated using author-reported raw data **FIB4: cut-off 2.67** TP 41 FP 10 FN 84 TN 406 Sensitivity 33% Specificity 98% Area under the curve 0.802 (0.758-0.847)
General limitations according to QUADAS II: The pathologist committee analysed the specimens in a blinded manner, but it is unclear whether the index test were interpreted without knowledge of the biopsy outcome as well. Liver biopsies were performed within 12 months prior to enrolment. It is unclear at what time the index tests were done, only that the data was chosen that was closest to liver biopsy time. Thresholds pre-defined.		

Study	**Shen 2012[868]**	
Study type	Retrospective analysis	
Number of studies (number of participants)	1 (n=147)	
Countries and Settings	Single-centre study at urban hospital in Hong Kong, China	
Funding	Study was supported by the General Research Fund of the Research Grant Council, Hong Kong	
Duration of study	2004 - 2010	
Age, gender, ethnicity	Mean age (SD): 47.7 (9.7), 55.8% Male. Ethnicity NR	
Patient characteristics	People with biopsy-proven Exclusions/exclusion criteria: NR Mean BMI (SD): 27.4 kg/m^2 (3.9); 47.6% had diabetes; 42.9% had hypertension; 74.8% had metabolic syndrome	
Index test	M30 Apoptense enzyme-linked immunosorbent assay ELISA kit. M65 ELISA kit	
Reference standard	Liver biopsy: percutaneous liver biopsy was performed using a 16G Temno needle.	
Target condition	NASH	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 203 U/L** TP 62 FP 53 FN 7 TN 25 Sensitivity 90%	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 338 U/L** TP 46 FP 31 FN 23 TN 47 Sensitivity 67%	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 670 U/L** TP 17 FP 8 FN 52 TN 70 Sensitivity 25%

Study	Shen 2012[868]		
Specificity 32% Area under the curve 0.66 (0.57-0.75)		Specificity 60% Area under the curve 0.66 (0.57-0.75)	Specificity 90% Area under the curve 0.66 (0.57-0.75)
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M65]: cut-off 501 U/L** TP 63 FP 51 FN 6 TN 27 Sensitivity 91% Specificity 35% Area under the curve 0.71 (0.62-0.79)		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M65]: cut-off 790 U/L** TP 43 FP 23 FN 26 TN 55 Sensitivity 62% Specificity 70% Area under the curve 0.71 (0.62-0.79)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M65]: cut-off 1183 U/L** TP 22 FP 8 FN 47 TN 70 Sensitivity 32% Specificity 90% Area under the curve 0.71 (0.62-0.79)
General limitations according to QUADAS II: this is a retrospective analysis of prospectively collected data. Patients were recruited consecutively. No information provided on exclusion criteria. Pathologists analysing the liver biopsy samples were blinded to clinical data. The index tests were done in a single session by one investigator, but it is unclear whether that investigator was blinded to the biopsy outcome. Thresholds were not pre-specified.			

Study	Sookoian 2009[899]
Study type	Cross-sectional study
Number of studies (number of participants)	1 (n=101)
Countries and Settings	Single-centre study at a county hospital in Buenos Aires, Argentina
Funding	Study was supported by a number of university and national research grants.
Duration of study	Not reported
Age, gender, ethnicity	Simple steatosis (n=41): mean age 52.3, 37% Male. Ethnicity NR

Study	Sookoian 2009[899]
	NASH (n=60): mean age 54.6, 28% male. Ethnicity NR
Patient characteristics	People with biopsy-proven NAFLD including ultrasonographic examinations suggestive of fatty infiltration performed by the same operator. Exclusions/exclusion criteria: secondary causes of steatosis, alcohol consumption of ≥ 30 g/d (men) or ≥ 20 g/d (women), total parenteral nutrition, hepatitis B or C, use of drugs known to cause steatosis Simple steatosis (n=41): mean BMI (SD) 32.1 kg/m^2 (5.3) NASH (n=60): mean BMI (SD) 33.7 kg/m^2 (6.6)
Index test	ALT levels
Reference standard	Liver biopsy: biopsy was performed using a modified 1.4 mm diameter Menghini needle on an outpatient basis. Specimens were routinely fixed in 40 g/L formaldehyde, embedded in paraffin and stained with hematoxylin-eosin, Masson trichrome and silver impregnation for reticular fibers. All biopsies were at least 2 cm in length and contained a minimum of 8 portal tracts.
Target condition	NASH
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: cut-off 22 U/L** TP 58 FP 31 FN 2 TN 10 Sensitivity 97% Specificity 24% Area under the curve 0.582 (0.479-0.680)	
General limitations according to QUADAS II: The pathologist was blinded to patient details. It is unclear how much time passed between the liver biopsy and the index tests. It is unclear whether people were enrolled consecutively. Thresholds were not pre-specified.	

Study	Sumida 2012[926]
Study type	Retrospective analysis of data from a large multi-centre study
Number of studies (number of participants)	1 (n=576)
Countries and Settings	Multi-centre study with 9 participating centres, Japan.
Funding	This study was supported by a grant from the Chiyoda Mutual Life Foundation.
Duration of study	2002 - 2008
Age, gender, ethnicity	Mean age (SD): 52.3 (15.4), 51% Male. Ethnicity NR
Patient characteristics	Patients with biopsy-confirmed NAFLD were enrolled from the Japan Study Group of NAFLD. Exclusions/exclusion criteria: viral hepatitis, autoimmune hepatitis, drug-induced liver disease, primary biliary cirrhosis, biliary obstruction, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, alcohol consumption of > 20 g/d, decompensated LC or HCC Mean BMI (SD): 27.9 (4.9), 73% were obese, 32% had hypertension, 42% had type-II diabetes
Index test	AST/ALT ratio APRI calculated using the formula: {[AST level/upper normal level (33 IU/L)]/[platelet count (10^9/L)]}*100 BARD score composed of 3 variables: score ranges from 0 to 4 points. AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point FIB4-index calculated using the formula: [age(years) * AST level]/[platelet count (10^9/L) * (ALT level)$^{1/2}$] NAFLD fibrosis score: -1.675 + 0.037 – age (years) + 0.094 – BMI + 1.13 * IFG/diabetes (yes = 1, no = 0) + 0.99 * AST/ALT ratio – 0.013 * platelet count (*10^9/L) – 0.66 * albumin (g/dL)
Reference standard	Liver biopsy: specimens were embedded in paraffin and stained with hematoxylin-eosin and Masson trichrome. The minimum biopsy size was 20 mm and the number of portal areas was 10.
Target condition	Advanced fibrosis

Study	Sumida 2012[926]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut-off 1** TP 43 FP 97 FN 21 TN 415 Sensitivity 67% Specificity 81% Area under the curve 0.823	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 0.8** TP 42 FP 123 FN 22 TN 389 Sensitivity 66% Specificity 76% Area under the curve 0.788	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 1** TP 31 FP 41 FN 33 TN 471 Sensitivity 48% Specificity 92% Area under the curve 0.788	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 51 FP 179 FN 13 TN 333 Sensitivity 80% Specificity 65% Area under the curve 0.765
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 1.45** TP 58 FP 184 FN 6 TN 328 Sensitivity 90% Specificity 64% Area under the curve 0.871	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 3.25** TP 31 FP 26 FN 33 TN 486 Sensitivity 48% Specificity 95% Area under the curve 0.871	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off -1.455** TP 59 FP 189 FN 5 TN 323 Sensitivity 92% Specificity 63% Area under the curve 0.863	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off 0.676** TP 21 FP 20 FN 43 TN 492 Sensitivity 33% Specificity 96% Area under the curve 0.863
General limitations according to QUADAS II: It is unclear whether patients were enrolled consecutively as retrospective nature of study design leads to concerns about patient selection. The two pathologists interpreting the biopsy specimens were blinded to clinical data. It is unclear whether the index tests were interpreted without knowledge of the biopsy outcome. Thresholds were pre-specified, based on published cut-offs.			

Study	Sumida 2012[926]
Study type	Retrospective analysis of pathology database
Number of studies (number of participants)	1 (n=222)
Countries and Settings	Single-centre study at a university medical centre, USA
Funding	Not reported
Duration of study	1 June 1995 – 30 June 2005
Age, gender, ethnicity	Normal ALT (n=56): Mean age (SD) 48.6 (10.8), 20% Male. Ethnicity 66.1% Caucasian Elevated ALT (n=166): mean age (SD) 44 (12.7), 49% Male. Ethnicity 67.3% Caucasian
Patient characteristics	Biopsy-proven NAFLD: Biopsy reports containing the terms steatosis, steatohepatitis and/or fat. All biopsies performed for abnormal liver appearance on imaging studies, or abnormal intra-operative findings during bariatric surgery or cholescystectomy were included irrespective of ALT levels. Exclusions/exclusion criteria: patients with other chronic liver disease (hepatitis B and C, iron over load, medication-related steatosis, alcohol consumption of ≥ 40 g/d in men or ≥ 20 g/d in women), liver transplant Normal ALT (n=56): mean BMI (SD) 40.7 kg/m^2 (12.4), 51.7% had type-II diabetes, 64.3% had hypertension, 65.4% had metabolic syndrome Elevated ALT (n=166): mean BMI (SD) 34.7 kg/m^2 (9), 26.4% had type-II diabetes, 43% had hypertension, 51% had metabolic syndrome
Index test	ALT levels
Reference standard	Liver biopsy: no biopsy methods reported.
Target condition	NASH

Study	Sumida 2012[926]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: cut-off 35 U/L** TP 48 FP 118 FN 6 TN 50 Sensitivity 89% Specificity 30% Area under the curve 0.62		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: cut-off 70 U/L** TP 27 FP 66 FN 27 TN 102 Sensitivity 50% Specificity 61% Area under the curve 0.62
General limitations according to QUADAS II: Retrospective nature of the research design raises concerns about patient selection. It is not clear when the biopsy was done and when the index tests were done. No information on biopsy methods or if patients were consecutive. Thresholds were not pre-specified.		

Study	Verma 2013[998]
Study type	Retrospective analysis of pathology database
Number of studies (number of participants)	1 (n=222)
Countries and Settings	Single-centre study at a university medical centre, USA
Funding	Not reported
Duration of study	1 June 1995 – 30 June 2005
Age, gender, ethnicity	Normal ALT (n=56): Mean age (SD) 48.6 (10.8), 20% Male. Ethnicity 66.1% Caucasian Elevated ALT (n=166): mean age (SD) 44 (12.7), 49% Male. Ethnicity 67.3% Caucasian
Patient characteristics	Biopsy-proven NAFLD: Biopsy reports containing the terms steatosis, steatohepatitis and/or fat. All biopsies performed for abnormal liver appearance on imaging studies, or abnormal intra-operative findings during bariatric surgery or cholescystectomy were included irrespective of ALT levels.

Study	Verma 2013[998]	
	Exclusions/exclusion criteria: patients with other chronic liver disease (hepatitis B and C, iron over load, medication-related steatosis, alcohol consumption of ≥ 40 g/d in men or ≥ 20 g/d in women), liver transplant Normal ALT (n=56): mean BMI (SD) 40.7 kg/m^2 (12.4), 51.7% had type-II diabetes, 64.3% had hypertension, 65.4% had metabolic syndrome Elevated ALT (n=166): mean BMI (SD) 34.7 kg/m^2 (9), 26.4% had type-II diabetes, 43% had hypertension, 51% had metabolic syndrome	
Index test	ALT levels	
Reference standard	Liver biopsy: no biopsy methods reported.	
Target condition	NASH	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: cut-off 35 U/L** TP 48 FP 118 FN 6 TN 50 Sensitivity 89% Specificity 30% Area under the curve 0.62		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **ALT: cut-off 70 U/L** TP 27 FP 66 FN 27 TN 102 Sensitivity 50% Specificity 61% Area under the curve 0.62
General limitations according to QUADAS II: Retrospective nature of the research design raises concerns about patient selection. It is not clear when the biopsy was done and when the index tests were done. No information on biopsy methods or if patients were consecutive. Thresholds were not pre-specified.		

Study	Wong 2008[1039]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=162)
Countries and Settings	China, multi-centre study at two liver and general medical clinics in Hong Kong
Funding	None declared
Duration of study	Dec 2004 – May 2007
Age, gender, ethnicity	Mean age (SD): 46 (10), 59% Male. Ethnicity NR
Patient characteristics	People with presence of fatty liver on imaging studies plus 1) persistent elevation of ALT above the upper limit of normal for two consecutive visits at least 12 weeks apart or, 2) risk factors for advanced fibrosis (e.g. obesity or diabetes). Exclusions/exclusion criteria: alcohol consumption of > 30 g/d (men) or > 20 g/d (women), coexisting liver disease (chronic viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, biliary obstruction, drug-induced liver disease), secondary causes of liver disease (corticosteroid use, gastric bypass) Mean BMI (SD): 28.5 kg/m^2 (4.4)
Index test	NAFLD fibrosis score: -1.675 + 0.037 – age (years) + 0.094 – BMI + 1.13 * IFG/diabetes (yes = 1, no = 0) + 0.99 * AST/ALT ratio – 0.013 * platelet count (*10^9/L) – 0.66 * albumin (g/dL)
Reference standard	Liver biopsy: liver biopsy was performed using a 16G Temno needle. Specimens were prepared with hematoxylin-eosin stain, Masson trichrome, Prussian blue, reticulin, orcein and periodic acid Schiff.
Target condition	Any fibrosis

Study	Wong 2008[1039]	
Results: 2x2 table calculated using author-reported raw data		Results: 2x2 table calculated using author-reported raw data
NAFLD fibrosis score: cut off -1.455		**NAFLD fibrosis score: cut off 0.676**
TP 7		TP 0
FP 27		FP 2
FN 11		FN 18
TN 117		TN 142
Sensitivity 39%		Sensitivity 0%
Specificity 81%		Specificity 99%
Area under the curve 0.64 (0.49-0.79)		Area under the curve 0.64 (0.49-0.79)
General limitations according to QUADAS II: it is unclear whether patients were enrolled consecutively. The histopathologists assessing the liver biopsy specimens were blinded to clinical data. It is unclear if the index tests were interpreted without knowledge of the liver biopsy outcome. Blood samples for the calculation of the index tests were taken on the day of the liver biopsy. Thresholds were pre-specified – based on published cut-offs.		

Study	Wong 2010[1038]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=246)
Countries and Settings	Multi-centre study with two participating hospitals in France and Hong Kong
Funding	Not reported
Duration of study	May 2003 – April 2009
Age, gender, ethnicity	Mean age (SD): 51 (11), 55% Male. Ethnicity 52% Caucasian, 48% Chinese
Patient characteristics	Adults with NAFLD. Exclusions/exclusion criteria: < 18 years of age, alcohol consumption of > 30 g/d (men) or > 20 g/d (women), secondary causes of hepatic steatosis (such as chronic use of systemic corticosteroids), positive hepatitis B surface antigen, anti-

Study	Wong 2010[1038]	
	hepatitis C virus antibody, histological evidence of other concomitant chronic liver diseases. 35/309 patients were excluded because liver biopsy length <15mm. 28/309 were excluded because of failure to obtain 10 valid LSM acquisitions. Patients who failed LSM had high BMI and waist circumference. Mean BMI (SD): 28.0 kg/m^2 (4.5), 36.2% had diabetes, 40.2% had hypertension	
Index test	Transient elastography performed within one week before liver biopsy. Measurements were performed on the right lobe of the liver through intercostal spaces with the patient lying in the dorsal decubitus with the right arm in maximal abduction. Ten successful acquisitions were performed on each patient. The median value represented the liver elastic modulus.	
Reference standard	Liver biopsy: the biopsies were performed using a 16G Temno or Menghini needle. The specimens were fixed in formalin and embedded in paraffin. The samples had a length of at least 15 mm.	
Target condition	Any fibrosis	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **TE: cut-off 7.9 kPa** TP 51 FP 47 FN 5 TN 143 Sensitivity 91% Specificity 75% Area under the curve 0.93 (0.89-0.96)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **TE: cut-off 8.7 kPa** TP 47 FP 32 FN 9 TN 158 Sensitivity 84% Specificity 83% Area under the curve 0.93 (0.89-0.96)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **TE: cut-off 9.6 kPa** TP 42 FP 16 FN 14 TN 174 Sensitivity 75% Specificity 92% Area under the curve 0.93 (0.89-0.96)
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. The histopathologists analysing the liver biopsy samples were blinded to the clinical data. The investigators were blinded to all clinical data and the patients' diagnosis. Transient elastography was performed one week before the biopsy. Thresholds were no pre-specified.		

Study	Wong 2012[1037]		
Study type	Prospective cohort		
Number of studies (number of participants)	1 (n=193)		
Countries and Settings	Multi-centre study at 2 participating hospitals in France and Hong Kong		
Funding	Study supported by the PROCORE-France/Hong Kong Joint Research Scheme and a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China		
Duration of study	Oct 2009 – Sep 2011		
Age, gender, ethnicity	Mean age (SD): 52 (11), 57% Male. Ethnicity 40% Caucasian, 60% Chinese		
Patient characteristics	Indications for liver biopsy included persistent abnormal liver biochemistry and the presence of risk factors of advanced disease such as type 2 diabetes. Exclusions/exclusion criteria: < 18 years of age, alcohol consumption of > 30 g/d (men) or > 20 g/d (women), secondary causes of hepatic steatosis (such as systemic corticosteroids and methotrexate), positive hepatitis B surface antigen, anti-hepatitis C virus antibodies, histological evidence of other concomitant liver disease. 12/205 patients were excluded because of liver biopsy <15mm. Mean BMI (SD): 28.9 kg/m^2 (4.8), 35% had BMI ≥30 kg/m^2 , 51% had type-II diabetes, 54% had hypertension, 75% had metabolic syndrome		
Index test	Transient elastography performed within 24 hours before liver biopsy. Measurements were performed on the right lobe of the liver through intercostal spaces with the patient lying in the dorsal decubitus with the right arm in maximal abduction. Ten successful acquisitions were performed on each patient. The median value represented the liver elastic modulus. In each person were measurements performed by the M probe followed by the XL probe. Reliable LSM results were obtained in 67% with M probe and 75% with XL probe.		
Reference standard	Liver biopsy: biopsies were performed using a 16G Temno or Menghini needle. Specimens were fixed in formalin and embedded in paraffin.		
Target condition	Any fibrosis		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence	Results: 2x2 table calculated using author-reported sens, spec and study prevalence	Results: 2x2 table calculated using author-reported sens, spec and study prevalence	

Study	Wong 2012[1037]		
TE [M probe]: cut-off 7.9 kPa TP 37 FP 36 FN 5 TN 78 Sensitivity 88% Specificity 68% Area under the curve 0.87 (0.82-0.93)	**TE [M probe]: cut-off 8.7 kPa** TP 35 FP 25 FN 7 TN 89 Sensitivity 83% Specificity 78% Area under the curve 0.87 (0.82-0.93)	**TE [M probe]: cut-off 9.6 kPa** TP 29 FP 18 FN 13 TN 96 Sensitivity 69% Specificity 84% Area under the curve 0.87 (0.82-0.93)
Results: 2x2 table calculated using author-reported sens, spec and study prevalence	Results: 2x2 table calculated using author-reported sens, spec and study prevalence	Results: 2x2 table calculated using author-reported sens, spec and study prevalence
TE [XL probe]: cut-off 5.7 kPa TP 49 FP 60 FN 5 TN 70 Sensitivity 91% Specificity 54% Area under the curve 0.85 (0.79-0.91)	**TE [XL probe]: cut-off 7.2 kPa** TP 42 FP 29 FN 12 TN 101 Sensitivity 78% Specificity 78% Area under the curve 0.85 (0.79-0.91)	**TE [XL probe]: cut-off 9.3 kPa** TP 31 FP 13 FN 23 TN 117 Sensitivity 57% Specificity 90% Area under the curve 0.85 (0.79-0.91)
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. Histopathologists assessing the biopsy specimens were blinded to clinical data. The transient elastography was performed within 24 hours before the biopsy. The investigators were blinded to clinical data and the patients' diagnosis. Thresholds were not pre-specified. Missing data based on failure of LSM.		

Study	**Xun 2012**[1052]	
Study type	Prospective cohort	
Number of studies (number of participants)	1 (n=152)	
Countries and Settings	Single-centre study at a university hospital, China	
Funding	Study supported by grants from the National Natural Science Foundation of China, National Basic Research Program of China, and the Municipal Commission of Science and Technology of Shanghai	
Duration of study	January 2005 – December 2010	
Age, gender, ethnicity	Mean age (±SD): 37.1 (±9.7), 79.6% Male. Ethnicity: Chinese Han	
Patient characteristics	Exclusions/exclusion criteria: alcohol consumption of > 140 g (men) or > 70 g (women) per week, concomitant viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, drug-induced hepatotoxicity, patients who had undergone repeated liver biopsies, inadequate biopsy specimens (, 15 mm in length with less than six portal tracts), patients undergoing therapeutic treatment Mean BMI (SD): 26.1 kg/m^2 (3.3), 25.7% were overweight, 59.2% were obese, 32.2% had type-II diabetes	
Index test	APRI (AST [ULN]/platelet count (*10^9/L)*100 AST/ALT ratio BARD weighted sum of three variables BMI ≥ 28 kg/m^2 = 1 point; AAR ≥0.8 = 2 points; T2D = 1 point. FIB4-index calculated using the formula: [age(years) * AST level]/[platelet count (10^9/L) * (ALT level)$^{1/2}$] NAFLD fibrosis score: -1.675 + 0.037 – age (years) + 0.094 – BMI + 1.13 * IFG/diabetes (yes = 1, no = 0) + 0.99 * AST/ALT ratio – 0.013 * platelet count (*10^9/L) – 0.66 * albumin (g/dL)	
Reference standard	Liver biopsy	
Target condition	Advanced fibrosis	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut-off 0.5** TP 19		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **APRI: cut-off 1** TP 10

Study	Xun 2012[1052]	
FP 64 FN 5 TN 64 Sensitivity 79% Specificity 50% Area under the curve 0.742 (0.624-0.860)		FP 15 FN 14 TN 113 Sensitivity 42% Specificity 88% Area under the curve 0.742 (0.624-0.860)
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 0.8** TP 10 FP 27 FN 14 TN 101 Sensitivity 42% Specificity 79% Area under the curve 0.670 (0.559-0.781)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 1** TP 6 FP 17 FN 18 TN 111 Sensitivity 25% Specificity 87% Area under the curve 0.670 (0.559-0.781)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 10 FP 27 FN 14 TN 101 Sensitivity 42% Specificity 79% Area under the curve 0.642 (0.513-0.771)
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 1.30** TP 16 FP 42 FN 8 TN 86 Sensitivity 67%	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 2.67** TP 9 FP 5 FN 15 TN 123 Sensitivity 37%	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 3.25** TP 5 FP 4 FN 19 TN 124 Sensitivity 21%

Study	Xun 2012[1052]	
Specificity 67% Area under the curve 0.756 (0.637-0.876)	Specificity 96% Area under the curve 0.756 (0.637-0.876)	Specificity 97% Area under the curve 0.756 (0.637-0.876)
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off -1.455** TP 9 FP 18 FN 15 TN 110 Sensitivity 37% Specificity 86% Area under the 0.653 (0.521-0.785)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off 0.676** TP 2 FP 1 FN 22 TN 128 Sensitivity 8% Specificity 100% Area under the curve 0.653 (0.521-0.785)	
General limitations according to QUADAS II: Patients were enrolled consecutively to this study. The histopathologist analysing the liver biopsy specimens was blinded to clinical data, but unclear if the opposite was also true. Clinical and laboratory data were obtained within 7 days before the liver biopsy. Thresholds based on published cut-offs.		

Study	Yilmaz 2007[1063]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=83)
Countries and Settings	Study setting is unclear, possibly single-centre study at a university hospital in Turkey
Funding	Not reported
Duration of study	November 2005 – October 2006
Age, gender, ethnicity	Mean age (SD): 48.9 (9.1), 54.2% Male. Ethnicity NR

Study	Yilmaz 2007[1063]	
Patient characteristics	People with NAFLD who were not using any medications (including estrogens, amiodarone, steroids, tamoxifen, or herbal supplements. Exclusions/exclusion criteria: viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha-1 antitrypsin deficiency, malignancies, alcohol consumption of > 20 g/d, previous abdominal surgery. Mean BMI (SD): 30.3 kg/m2 (4.8), 33.7% had hypertension, 34.9% had metabolic syndrome, 14.5% had diabetes	
Index test	Serum levels of M30-antigen and M65-antigen determined by commercially available immunoassays. M30-Apoptosense ELISA kit and M65 ELISA kit).	
Reference standard	Liver biopsy: biopsies performed using a 16G Klatskin needle. The length of the specimens was not smaller than 2.5 cm. All specimens were fixed in formalin and embedded in paraffin. Serial sections were stained with hematoxylin-eosin and Masson's trichrome.	
Target condition	NASH	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M30]: cut-off 121.1 IU/L** TP 27 FP 1 FN 18 TN 37 Sensitivity 60% Specificity 97% Area under the curve 0.787 (0.683-0.869)	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **CK 18 [M65]: cut-off 243.82 IU/L** TP 31 FP 7 FN 14 TN 31 Sensitivity 69% Specificity 82% Area under the curve 0.809 (0.708-0.887)	
General limitations according to QUADAS II: It is unclear whether patients were enrolled consecutively to this study. The pathologist analysing the biopsy specimens was blinded to clinical data. It is unclear when the index tests were done in relation to the liver biopsy. The index tests were analysed in a blinded fashion. Thresholds were not pre-specified.		

Study	Yoneda 2008[1069]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=97)
Countries and Settings	Multi-centre study with 2 participating hospitals, Japan
Funding	Study was supported by a Grant-in-Aid from the Ministry of Health, a grant from the Ministry of Education, and a grant from the National Institute of Biomedical Innovation.
Duration of study	Not reported
Age, gender, ethnicity	Mean age (SD): 51.8 (13.7), 41% Male. Ethnicity NR
Patient characteristics	NASH patients who underwent liver biopsy: presence of NAFLD based on macrovesicular fatty change in hepatocytes with displacement of the nucleus to the edge of the cell. Exclusions/exclusion criteria: history of hepatic disease (chronic hepatitis C or concurrent active hepatitis B infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, hepatic injury caused by substance abuse), alcohol consumption of > 20 g/d. 5/102 patients were excluded because of unreliable LSM. All five had BMI >30. Mean BMI (SD): 26.6 kg/m^2 (4.2)
Index test	Transient elastography performed with Fibroscan. Measurements were performed in the right lobe of the liver through the intercostal spaces, with the patients lying in the dorsal decubitus position with their right arm in maximal abduction on a portion of the liver that is at least 6cm thick and free of large vascular structures. The measurement depth is between 25-45mm. Ten successful acquisitions are performed on each patient. The success rate is calculated as the ratio of the number of successful acquisitions to that of the total number of acquisitions and a success rate of at least 60% or the IQR <30% were considered reliable. The median value was determined as representative of the liver elastic modulus. TE was performed within 3 months before and after biopsy.
Reference standard	Liver biopsy: biopsies were performed using an 18G needle. A minim of seven portal tracts and a minimum length of 20 mm were required. The specimens were stained in hematoxylin-eosin, reticulin and Masson trichrome stains.
Target condition	Any fibrosis and advanced fibrosis

Study	Yoneda 2008[1069]	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **TE: cut-off 5.90 kPa** TP 68 FP 2 FN 11 TN 16 Sensitivity 86% Specificity 89% Area under the curve 0.927		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **TE: cut-off 9.80 kPa** TP 23 FP 13 FN 4 TN 57 Sensitivity 85% Specificity 81% Area under the curve 0.904
General limitations according to QUADAS II: It is unclear whether patients were enrolled consecutively to this study. Unclear whether the population was NAFLD or NASH. The two pathologists analysed the biopsy specimens independently and were blinded to the clinical data. The FibroScan was done within three months before and after the liver biopsy. It is unclear if the investigators performing the FibroScan were blinded to clinical data and/or the liver biopsy outcome. Thresholds were no pre-determined.		

Study	Yoneda 2010[1070]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=54)
Countries and Settings	Single-centre study at an urban university hospital, Japan
Funding	Study was supported by a Collaborative Development of Innovative Seeds programme grant from the Japan Science and Technology Agency, a grant from the National Institute of Biomedical Innovation, and a grant from the Yokohama Foundation for Advancement of Medical Science.
Duration of study	Jan 2009; patients recruited based on their visit to the hospital between Jan 2008 – Dec 2008,
Age, gender, ethnicity	Male patients (n=25): mean age (SD) 48.3 (13.5), Ethnicity NR

Study	Yoneda 2010[1070]
	Female patients (n=29): mean age (SD) 52.5 (11.4), Ethnicity NR
Patient characteristics	NAFLD patients who underwent liver biopsy: presence of NAFLD based on macrovesicular fatty change in hepatocytes with displacement of the nucleus to the edge of the cell. Exclusions/exclusion criteria: history of hepatic disease (chronic hepatitis C or concurrent active hepatitis B infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, hepatic injury caused by substance abuse), alcohol consumption of > 20 g/d Male patients (n=25): mean BMI (SD) 28.2 kg/m^2 (5) Female patients (n=29): mean BMI (SD) 26.2 kg/m^2 (4.4)
Index test	ARFI sonoelastography performed using a Siemens Acuson S2000 US system. ARFI was performed with a curved array US probe at 4 MHz for B-mode imaging. The right lobe of the liver was examined through the intercostal space with the patient lying in a dorsal decubitus position with the right arm in maximal abduction. An area where the liver tissue was at least 6cm thick and free of large blood vessels was chosen. A measurement depth of 2cm below the liver capsule was chosen to standardise the examination. Ten successful acquisitions were performed in each patient, and the median value was getermined and used as a preresentative measurement of the liver elastic modulus. Transient elastography performed with Fibroscan. Measurements were performed in the right lobe of the liver through the intercostal spaces, with the patients lying in the dorsal decubitus position with their right arm in maximal abduction on a portion of the liver that is at least 6cm thick and free of large vascular structures. The measurement depth is between 25-45mm. Ten successful acquisitions are performed on each patient. The success rate is calculated as the ratio of the number of successful acquisitions to that of the total number of acquisitions and a success rate of at least 60% or the IQR <30% were considered reliable.
Reference standard	Liver biopsy: biopsies were performed using an 18G needle. A minimum of seven portal tracts and a minimum length of 20 mm were required. The specimens were stained with hematoxylin-eosin, reticulin and Masson trichrome stains.
Target condition	Advanced fibrosis

Study	Yoneda 2010[1070]	
Results: 2x2 table calculated using author-reported raw data		Results: 2x2 table calculated using author-reported raw data
ARFI: cut-off 1.77 m/s		**TE: cut-off 9.9 kPa**
TP 10		TP 10
FP 4		FP 3
FN 0		FN 0
TN 40		TN 41
Sensitivity 100%		Sensitivity 100%
Specificity 91%		Specificity 93%
Area under the curve 0.973		Area under the curve 0.990
General limitations according to QUADAS II: Patients were recruited consecutively. The pathologist analysing the biopsy specimens and the physician performing the index tests was blinded to clinical data. ARFI was performed within 12 months of the liver biopsy (mean interval 5.8months (SD 3.6). Thresholds were not pre-specified.		

Study	Yoneda 2013[1068]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=235)
Countries and Settings	Multi-centre study with ten participating hepatology centres in Japan
Funding	Study was supported by a Grant-in-Aid from the Ministry of Education, a grant from the Chiyoda Mutual Life Foundation and by a Thrust Area Research Grant from Osaka City University
Duration of study	2002 - 2011
Age, gender, ethnicity	Mean age (SD): 59.9 (12.1), Sex NR, Ethnicity NR
Patient characteristics	People with biopsy-proven NAFLD and normal ALT levels (patients with ALT ≤ 40 U/L) Exclusions/exclusion criteria: history of hepatic disease (chronic hepatitis C or concurrent active hepatitis B infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, hemochromatosis, alpha-1 antitrypsin

Study	Yoneda 2013[1068]	
	deficiency, Wilson's disease, hepatic injury caused by substance abuse), alcohol consumption of > 20 g/d Mean BMI (SD): 26.9kg/m^2 (4.0), 63.8% had dyslipidaemia, 46% had diabetes	
Index test	AST/ALT ratio BARD score composed of 3 variables: score ranges from 0 to 4 points. AST/ALT ratio ≥ 0.8: 2 points; BMI ≥ 28: 1 point; Presence of diabetes: 1 point. FIB4-index calculated using the formula: [age(years) * AST level]/[platelet count (10^9/L) * (ALT level)$^{1/2}$] NAFLD fibrosis score: -1.675 + 0.037 – age (years) + 0.094 – BMI + 1.13 * IFG/diabetes (yes = 1, no = 0) + 0.99 * AST/ALT ratio – 0.013 * platelet count (*10^9/L) – 0.66 * albumin (g/dL)	
Reference standard	Liver biopsy: no further details supplied	
Target condition	Advanced fibrosis	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 0.8** TP 34 FP 124 FN 4 TN 73 Sensitivity 89% Specificity 37% Area under the curve 0.794	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **AST/ALT ratio: cut-off 0.975** TP 30 FP 59 FN 8 TN 138 Sensitivity 79% Specificity 70% Area under the curve 0.794	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **BARD: cut-off 2** TP 33 FP 133 FN 5 TN 64 Sensitivity 87% Specificity 32% Area under the curve 0.671

Study	Yoneda 2013[1068]		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 2.67** TP 24 FP 23 FN 14 TN 174 Sensitivity 63% Specificity 88% Area under the curve 0.878	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **FIB4: cut-off 1.659** TP 34 FP 57 FN 4 TN 140 Sensitivity 89% Specificity 71% Area under the curve 0.878	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off 0.676** TP 26 FP 24 FN 12 TN 173 Sensitivity 68% Specificity 88% Area under the curve 0.843	Results: 2x2 table calculated using author-reported sens, spec and study prevalence **NAFLD fibrosis score: cut-off 0.735** TP 26 FP 23 FN 12 TN 174 Sensitivity 68% Specificity 88% Area under the curve 0.843
General limitations according to QUADAS II: It is unclear whether patients were recruited consecutively. It is unclear whether the index tests were analysed without knowledge of the liver biopsy outcome and vice versa. It is also unclear when the biopsy and the index tests were done. No method information for liver biopsy. Thresholds based on published cut-offs and then reported at thresholds not pre-determined.			

Study	Yoneda 2015[1071]
Study type	Retrospective analysis
Number of studies (number of participants)	1 (n=1201)
Countries and Settings	Multi-centre study with nine participating hepatology centres in Japan
Funding	None declared
Duration of study	2001 - 2013
Age, gender, ethnicity	Mean age (SD): 50.8 (15), 53% Male. Ethnicity NR
Patient characteristics	Exclusions/exclusion criteria: NR

Study	Yoneda 2015[1071]	
Index test	Serum ferritin levels	
Reference standard	Liver biopsy: no further information reported.	
Target condition	Any fibrosis and advanced fibrosis	
Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Any fibrosis** **Ferritin: cut-off 208.8 ng/mL** TP 479 FP 69 FN 494 TN 159 Sensitivity 49% Specificity 70% Area under the curve 0.617		Results: 2x2 table calculated using author-reported sens, spec and study prevalence **Advanced fibrosis** **Ferritin: cut-off 301 ng/mL** TP 90 FP 235 FN 179 TN 697 Sensitivity 33% Specificity 75% Area under the curve 0.554
General limitations according to QUADAS II: it is unclear if the index test was interpreted without knowledge of the biopsy outcome or vice versa. It is also unclear when the index test and the biopsy were done. Short communication and retrospective nature of this report leads to concerns about patient selection as no details provided.		

Study	Younossi 2011[1076]
Study type	Retrospective analysis
Number of studies (number of participants)	1 (n=79)
Countries and Settings	Single-centre study at an urban hospital, USA
Funding	Study was supported by the Liver Disease Outcomes Fund of the Centre for Liver Diseases at Inova Fairfax Hospital, Inova Health system

Study	**Younossi 2011[1076]**		
Duration of study	Not reported		
Age, gender, ethnicity	Mean age (SD): 42.32 (10.26), 22.8% Male. Ethnicity 69.2% Caucasian		
Patient characteristics	People with histologically proven NAFLD. Exclusions/exclusion criteria: alcohol consumption of ≥ 10 g/d, other causes of liver disease (hepatitis B or C, autoimmune hepatitis), patients receiving treatment with PPAR-γ agonists Mean BMI (SD): 47.56 kg/m^2 (8.07), 24.4% had diabetes		
Index test	Fasting serum specimens obtained at the time of biopsy and stored at -80° CK 18 (M65 antigen a measurement of overall cell death due to both apoptosis and necrosis) and capase-cleaved CK 18 (M30 antigen, a specific measurement of apoptosis) were profiled by M65 and M30 ELISA kits.		
Reference standard	Liver biopsy: specimens were fixed in formalin and stained with hematoxylin-eosin and Masson trichrome.		
Target condition	NASH		
Results: 2x2 table calculated using author-reported sens, spec and study prevalence	Results: 2x2 table calculated using author-reported sens, spec and study prevalence	Results: 2x2 table calculated using author-reported sens, spec and study prevalence	
CK 18 [M30]: cut-off 200.543	**CK 18 [M30]: cut-off 272.924**	**CK 18 [M30]: cut-off 537.062**	
TP 36	TP 29	TP 11	
FP 26	FP 14	FP 5	
FN 4	FN 11	FN 29	
TN 13	TN 25	TN 34	
Sensitivity 90%	Sensitivity 72%	Sensitivity 27%	
Specificity 33%	Specificity 64%	Specificity 87%	
Area under the curve 0.71 (0.60-0.81)	Area under the curve 0.71 (0.60-0.81)	Area under the curve 0.71 (0.60-0.81)	
General limitations according to QUADAS II: Retrospective nature of the research design leads to concerns around patient selection. The hepatopathologist was blinded to all clinical and laboratory data. It is unclear if the index tests were interpreted without knowledge of the liver biopsy outcome. Serum specimens were taken at the time of the liver biopsy. Results only reported for M30 not M65.			

H.4 Monitoring NAFLD progression

Reference	Adams 2005 [14]
Study type and analysis	Retrospective longitudinal study
Setting	USA
Number of participants and characteristics	n=103 Inclusion criteria: All people who had a diagnosis of NAFLD and had undergone more than one liver biopsy, ethanol consumption of less than 140g/week Exclusion criteria: People with evidence of other liver disease using standard clinical, laboratory and histological criteria. People where there was a secondary cause of NAFLD Recruited: from one hospital database Median age: 45 +/- 11 years (median) Gender: 63% female n.b: 26/103 people had a repeat biopsy as medically indicated, 77/103 had the repeat biopsy as part of a placebo arm in a RCT with target populations of NALFD. One patient increased her alcohol consumption to an average of 30-40 mg/day between biopsies. One patient was initially on metformin and continued on the same dose. No patients were taking thiazolidinedione's or vitamin E. NAFLD: Steatosis involving at least 10% of hepatocytes on biopsy NAFL: Combination of Steatosis with nonspecific inflammation (Steatosis plus either lobular inflammation or ballooning but not both) or bland Steatosis (Steatosis without lobular inflammation ballooning or fibrosis) NASH: presence of Steatosis plus mixed lobular inflammation plus hepatocellular ballooning necrosis or the presence of Steatosis plus any stage of fibrosis.
Prognostic variable(s)	Liver biopsy: minimum 15 mm in length, analysed using Brunt's criteria and also commenting on Ballooning, Mallory's hyaline, and hepatocellular iron. Predictors of fibrosis rate: AST/ALT ratio- measured on serology Age Steatosis grade- measured on initial liver biopsy

Reference	Adams 2005 [14]
	BMI Diabetes- not defined Fibrosis stage – measured on initial liver biopsy
Confounders OR stratification strategy	Fibrosis rate calculated by dividing the difference in fibrosis stage between first and last biopsy, by the time between the biopsies in years. Univariate and multivariate analysis using linear regression analysis for predictors of rate of progression.
Outcomes and effect sizes	Mean follow up was 3.2 +/- 3.0 years. Mean rate of fibrosis progression: 0.02 +/- 0.66 stages/year, range -2.05 to 1.70 stage/year. If people with cirrhosis were excluded the rate of fibrosis change was 0.09 +/- 0.67 stages/year. 37% (n=38) patients increased in fibrosis stage between first and last biopsy 34% (n=35) patients remained stable in fibrosis stage between first and last biopsy 29% (n=30) patients regressed in fibrosis stage between first and last biopsy The proportion of people with NASH on initial biopsy who had later fibrosis progression was 34.4%
	Univariate linear regression analysis: Diabetes p=0.01 AST/ALT ratio p=0.02 Fibrosis stage on initial biopsy p= 0.003 Multivariate analysis- adjusted for AST/ALT ratio, age, Steatosis grade, BMI, diabetes, fibrosis stage : Diabetes: 0.005 Early fibrosis stage: 0.001 BMI: 0.008
Comments	High risk of bias. This paper uses data from RCT, including both the active and control group for trials with ursodiol and clofibrate, were there were no significant differences found.

Reference	Chan 2014[183]
Study type and analysis	Prospective observational study

Reference	Chan 2014[183]
Setting	Kuala Lumpur
Number of participants and characteristics	n= 75 (39 had serial biopsies) Inclusion: Biopsy proven NAFLD. Exclusion: not clear in report, but presumed excluded if had significant alcohol intake, or serology proved viral hepatitis. Mean age (at follow-up) 50.5 +/- 12 years Gender- 8 male:31 female Definitions of NAFLD, NAFL and NASH not possible to extract from the paper.
Prognostic variable(s)	417eHistological assessment of paired liver biopsy, by a single histopathologist who was blinded to the clinical data and the biopsy sequence. Assessment made using the non- alcoholic steatohepatitis clinical research network scoring system. mean number of portral tracts in the original sample was 8.6 +/- 4.4, and in the follow up 6.6 +/- 4.6 Other variables measured to see if they affect the fibrosis progression included age, BMI, gender, ethnicity and serological tests: Hb1AC Fasting blood sugar Lipid profile Liver function tests
Confounders OR stratification strategy	Univariate and multivariate analysis performed to identify factors that were associated with worsened NAS and liver fibrosis. No details provided on which tests were used. There were no details provided on which factors were used.
Outcomes and effect sizes	Mean follow-up time 6.4+/- 0.8 years • fibrosis progression: 18 (46%) • stable: 17 (44%) • fibrosis regression: 4 (10%)
	Multivariate analysis- not reported adequately enough to extract, but no significant factors found.
Comments	Very high risk of bias. Large attrition rate and information in methods on definitions and inclusion/exclusion criteria not reported.

Reference	Ekstedt 2012 [272]
Study type and analysis	Prospective observational study
Setting	Sweden
Number of participants and characteristics	n= 129, (total included=68, 25 people died prior to follow up, 38 people either did not accept re-evaluation, or repeated biopsy, 2 of which were in clinical liver failure) Inclusion: People with NAFLD Exclusion: alcohol consumption>140 g/week, any medication associated with fatty infiltration of the liver. NAFLD: Hepatic Steatosis without any other concomitant liver disease. NAFL: Simple Steatosis or Steatosis with nonspecific inflammation and absence of fibrosis NASH: Steatosis plus any stage of fibrosis, or as Steatosis plus lobular inflammation and hepatocellular ballooning degeneration.
Prognostic variable(s)	Liver biopsy: graded by one histopathologist using Brunt's criteria. Significant fibrosis progression was defined as progression of more than one fibrosis stage or development of end stage liver disease at follow up.
Confounders OR stratification strategy	Univariate and multivariate analysis using logistic regression analysis done for associations between histopathological variables and significant fibrosis progression. Significant fibrosis progression defined as >1 stage of fibrosis increase from baseline biopsy. Factors included: Steatosis grade Portal inflammation Hepatocellular ballooning Mallory bodies Portal fibrosis stage Perisinsoidal fibrosis stage NAS
Outcomes and effect sizes	Mean follow up time was 13.8 +/- 1.2 years (range 10.3-16.3 years) • worse: 29 • Stable:30 • Improved: 11
	Multivariate analysis No histopathological factors were found to be significantly associated with fibrosis progression
Comments	High risk of bias. High attrition rate. Two people were included in the review without further biopsy that had developed ascites and been diagnosed with hepatocellular carcinoma at follow up. They were assumed to have progressed a stage in fibrosis.

Reference	Ekstedt 2012 [272]
Reference	Evans [284]
Study type and analysis	Prospective observational study
Setting	UK
Number of participants and characteristics	n= 62 people (only 7 had repeat biopsies) Inclusion criteria: all people with NASH diagnosed over a ten year period were called back >3 years post diagnosis for review. They were screened for alcohol and other causes of liver disease. Mean age:50.9 years Gender: 6 males: 20 females NASH- Non-alcoholic Steatosis with necroinflammation and/or fibrosis
Prognostic variable(s)	NAFLD progression in disease from a liver biopsy analysed using Brunt scoring by a single pathologist, and then scored blind by another pathologist for reliability assessment.
Confounders OR stratification strategy	No information provided on factors associated with progression of fibrosis
Outcomes and effect sizes	Median follow up was 8.2 years No significant difference between baseline fibrosis and follow up. The fibrosis progression was 0.088 fibrosis unit/year.
Comments	High risk. No information given on the indication for repeat biopsy given, and only a small subset went on to have the repeat biopsy.

Reference	Fassio 2004[294]
Study type and analysis	Prospective observational study
Setting	Argentina
Number of participants and characteristics	n= 22 people (41 people initially, but 19 declined to participate or could not be contacted). Inclusion criteria: NASH diagnosis, plus a span of 3 or more years since initial liver biopsy. Exclusion criteria: concomitant medication that can cause NASH.

Reference	Fassio 2004[294]
	Concomitant treatments: all people referred to nutritional department for the treatment of metabolic disorders but no treatment for NASH was given to any people. Median age: 45 years (range 20-69) Gender: 9 males: 13 females NASH- characteristic features in the liver biopsy, including macrovesicular Steatosis (>10% of hepatocytes) and lobular inflammation plus ballooning degeneration, Mallory hyaline fibrosis, sinusoidal fibrosis, or a combination thereof. Persistently abnormal alanine aminotransferase (ALT) levels and/or aspartate aminotransferase (AST) levels. Alcohol intake of less than 40 gin men and less than 20 g in women as self-reported and close family member verified. Appropriate exclusion of other causes of chronic liver disease including hepatitis B and C, autoimmune hepatitis, drug induced hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease.
Prognostic variable(s)	NAFLD progression in disease from a liver biopsy, minimum 25 mm in length. All specimens examined blind and not with the paired earlier test. Brunt and Ishak classifications were used. Progression of liver fibrosis was defined as an increase 1 grade or more in the final stage with respect to the basal biopsy in either classification system.
Confounders OR stratification strategy	univariate analysis only of factors associated with fibrosis progression.
Outcomes and effect sizes	median follow up was 4.3 years (range 3.0-14.3) years • Stable= 15 (68.2%) Worse= 7 (31.8%)ibrosis progression= 0.059 fibrosis units per year
Comments	High attrition rate, although there were no statistical differences in baseline between those who dropped out.

Reference	Feldstein 2005 [299]
Study type and analysis	Retrospective longitudinal study
Setting	USA
Number of participants and characteristics	n=39 Inclusion criteria: diagnosis of NAFLD confirmed on baseline liver biopsy, and showing no stage 0 or mild (stage 1-2) fibrosis on Brunt's scale, ethanol consumption of less than 140 g/week, exclusion of other liver diseases, those who had a repeat biopsy within 60 months of the original biopsy, and the original biopsy was available for comparison.

Reference	Feldstein 2005 [299]
	Median age: 45 +/- 10years Gender: 18 males:21 females NAFLD- steatosis of at least 10 % hepatocytes
Prognostic variable(s)	NAFLD progression in disease from a liver biopsy, minimum 15mm. The single pathologist who analysed these was blind to the original samples. Staging was done using Brunt's criteria. Change was defined as 1 stage of fibrosis or more.
Confounders OR stratification strategy	No multivariate analysis of factors affecting fibrosis progression
Outcomes and effect sizes	Median follow up was 22 (SD: 13 months, range 5-59 months) • No fibrosis progression=17 (44%) • Fibrosis progression =22 (56%)
Comments	High risk of bias. No information is given on why repeat biopsies were ordered or how other liver disease was excluded.

Reference	H A-Kader 2008 [420]
Study type and analysis	Retrospective longitudinal study
Setting	USA
Number of participants and characteristics	n=106, a subset 18 of which had repeat liver biopsy undertaken for clinical indications Inclusion criteria: NAFLD confirmed by liver biopsy, and other causes rules out via clinical findings and histology Nb. No patients received any therapy in between the biopsies besides weight loss counselling and increased physical activity. BMI increased in the time period. Mean age: Range 7-19 Gender: 17 males: 1 females
Prognostic variable(s)	NAFLD progression in disease from a liver biopsy analysed using Brunt scoring.
Confounders OR stratification strategy	No multivariate analysis of factors affecting fibrosis progression

Reference	H A-Kader 2008 [420]
Outcomes and effect sizes	median follow up was 28 months fibrosis progression=7 (39%) improvement in fibrosis=3 (17%) stable= 8 (44%)
Comments	No information given on the indication for repeat biopsy given, and only a small subset went on to have the repeat biopsy.

Reference	Hamaguchi 2010 [385]
Study type and analysis	Prospective observational study
Setting	Japan
Number of participants and characteristics	n= 39 people Inclusion criteria: subjects who underwent serial liver biopsies with NAFLD in one teaching hospital. Nb. None of the people were on concomitant treatments Median age: 47 range (20-79) years Gender: 22 males: 17 females NAFLD- Hepatic Steatosis in the absence of known causes of fatty liver NAFL- Hepatic Steatosis without presence of ballooned hepatocytes NASH-Hepatic Steatosis along with ballooned hepatocytes with lobular hepatitis
Prognostic variable(s)	NAFLD progression in disease from a liver biopsy analysed using Brunt scoring by a single pathologist on two occasions who was blinded to the clinical information and the order in which the biopsies were taken.
Confounders OR stratification strategy	Multivariate adjusted hazard ratios for improving liver fibrosis were calculated using Cox proportional hazard model. The variables tested included diabetes, BMI, dyslipidaemia, treatment with insulin, HbA1C (higher >1%), treatment with ARB. They were adjusted for : age gender BMI factors that were significant associated were added into the analysis
Outcomes and effect sizes	median follow up was 2.4 years (range 1.0-8.5 years)

Reference	Hamaguchi 2010 [385]
	• Improved: 12 (31%) • Stable: 16 (41%) • Progressed: 11 (28%)
	Multivariate analysis of factors associated with improving fibrosis change in HbA1C - risk ratio 0.18 (95%CI 0.05-0.59), p value 0.01 treatment with insulin- risk ratio 0.03 (95% CI 1.20-61.59), p value 0.03
Comments	High risk- A large attrition rate (67 refused biopsies). Large confidence interval on risk ratios for association with improvement of fibrosis.

Reference	Harrison 2003 [399]
Study type and analysis	Prospective observational study
Setting	USA
Number of participants and characteristics	n=128 identified, but only 22 included in study. Most due to nonattendance or refusal to take part. Inclusion criteria: NASH on initial biopsy, other screens of liver disease were negative. Exclusion criteria: initial biopsy report indicating age>65 or <18, autopsy specimens, post liver transplantation, alcohol abuse, cancer (liver primary or metastatic) or methotrexate use. Concurrent diagnosis that could significantly affect liver histology. Recruited- from a database of an army medical centre, but then added in extra people that were known to meet the criteria but not specified a priori. Median age: 41.8 +/- 2.6 years Gender:11 males:6 females
Prognostic variable(s)	NAFLD progression in disease from a liver biopsy, which was analysed by a single pathologist, blinded to the patient history and sequence of biopsies examined. A modified Brunt's criteria was used for inflammation and hepatocyte degeneration and necrosis. The Brunt's score for fibrosis was used normally.
Confounders OR stratification strategy	univariate analysis only of factors associated with fibrosis progression.
Outcomes and effect sizes	median follow up was 5.7 (range 1.4-15.7) years • Worse= 7 (32%)

Reference	Harrison 2003 [399]
	• Stable= 11 (50%) • Improved = 4 (18%)
Comments	High risk. Very high rate of attrition.

Reference	Hui 2005 [438]
Study type and analysis	Prospective observational study
Setting	Hong Kong
Number of participants and characteristics	n=17 Inclusion criteria: all people who had liver biopsies in the previous 3 years in one hospital medical registry with evidence of NAFLD Exclusion criteria: evidence of chronic hepatitis B, C, autoimmune hepatitis, Wilson's disease, haemochromotosis, and drug related hepatitis, and alcohol consumption of less than 20g/week. Taken from medical notes reviewed by two clinicians. Median age: 41.8 +/- 2.6 years Gender:11 males:6 females Nb- During the follow up period people were given treatment for hypertension and diabetes and advice on weight loss. No patients were given lipid lowering drugs. Drugs known to be associated with NAFLD or NASH were not given to any people. NAFLD- Histologic evidence of steatosis with or without the presence of necroinflamation and fibrosis. NAFL- Hepatic steatosis without necroinflamation or fibrosis. NASH- Hepatic steatosis with some necroinflammatory activity and/or fibrosis.
Prognostic variable(s)	NAFLD progression in disease from a liver biopsy, minimum 15mm, with at least 5 portal tracts. The pathologist who analysed these was blind to the original samples. Staging was done using a modified Brunt's criteria, from 0-4, with stage 0 indicating absent inflammation and fibrosis respectively. Change was defined as 1 stage or more in the Brunt's criteria.
Confounders OR stratification strategy	univariate analysis of factors affecting fibrosis progression only.
Outcomes and effect sizes	median follow up was 6.1 (range -3.8-8.0) years • Stable= 8 (47%)

Reference	Hui 2005 [438]
	• Worse= 9 (53%) This was mainly due to worsening in fibrosis, as there was no significant change between the two biopsies in macrovascular steatosis and necroinflammation scores.
Comments	High risk of bias. Small population.

Reference	McPherson 2014[650]
Study type and analysis	retrospective longitudinal study
Setting	UK
Number of participants and characteristics	n= 108 Inclusion criteria: people with 2 or more liver biopsies taken at least 1 year apart (the first and last biopsies if more than 2 taken, or pre-treatment biopsy if entered into a treatment trial). Exclusion criteria- People with alternative liver diagnosis or evidence of coexistent liver disease, people who consumed more than 30 g alcohol/day for me, or 20g alcohol/day for women. Recruited- tertiary NAFLD clinic nb. five people were treated with type 2 diabetes and NASH were treated with pioglitazone. No one received vitamin E. Mean age = 48 +/- 12 Gender= 66% male: 44% female NAFLD- Steatosis affecting 5% of hepatocytes in the absence of excessive significant alcohol consumption, other liver disease or the consumption of steatogenic drugs. NAFL- Steatosis without hepatocellular injury NASH- Steatosis with inflammation and hepatocyte ballooning degeneration +/- fibrosis
Prognostic variable(s)	Histological assessment of liver biopsies, all 15 mm in length. Read by one experienced hepatopathologist. Scoring undertaken using the NASH CRN score and the NAFLD activity score= (NAFLD score-=-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl). The rate of fibrosis was calculated.
Confounders OR stratification strategy	Univariate analysis was performed using paired t tests. Any factors that were significant were included in a multivariate analysis. The factors from baseline and follow-up were analysed separately with different factors included in the analysis

Reference	McPherson 2014[650]
Outcomes and effect sizes	Median follow up time 6.6 years range 1.3-22.6 years (68% >5 years) fibrosis progression rate: 0.08 +/- stages/year. fibrosis progression rate in those who progressed in fibrosis: 0.29 +/- 0.24 stages/year • progression of fibrosis = 45 (42%) • stable= 43 (40%) • regression of fibrosis= 20 (18%) Of the people who progressed: 1 stage= 26 2 stages= 15 3 stages=4 Of the people who regressed: 1 stage=17 3 stages=3
	Multivariate analysis of factors at baseline that were associated with progressed fibrosis (accounting for platelet count, AST/ALT ratio and FIB-4(FIB4= age [years] × AST [IU/L]/platelet count [expressed as platelets × 109/L] × (ALT1/2[IU/L])): FIB-4 score- OR 2.1, CI 1.1-3.9, p=0.019 (AUROC= 0.63, CI 0.51-0.76, p=0.036) Multivariate analysis of factors at follow up that were associated with progressed fibrosis (accounting for type 2 diabetes mellitis, platelet count, GGT, AST/ALT ratio, FIB-4 score, NAFLD fibrosis score): The Presence of type 2 diabetes mellitis- OR 6.25 CI 1.88-20, p=0.003 FIB-4 score- OR 3.1, CI 1.4-6.8 , p=0.04
Comments	High risk of bias. No information on treatment modifying intervention between biopsies, and poor information on the histological assessment, not reporting whether the assessor was blinded, or whether samples were reported by multiple assessors.

Reference	Pais 2013[733]
Study type and analysis	Retrospective longitudinal study

Reference	Pais 2013[733]
Setting	France
Number of participants and characteristics	n= 70 Inclusion: all adult people diagnosed with primary NAFLD who had undergone a repeat liver biopsy one year or more after the index biopsy Exclusion: Alcohol intake higher than 30g/day for men, and 20 g/day for women, exposure to drugs that can cause steatosis, people with other liver disease including viral and autoimmune aetiologies. nb. the main reasons for follow up liver biopsy were persistent ALT elevation along with persistent or elevated metabolic risk factors, as a requirement of inclusion in clinical trials, and the inability to successfully implement dietary and lifestyle changes. People who significant lost weight during follow up did not undergo a control liver biopsy. Mean age: 52 +/-10.5 Gender: not reported NAFLD- steatosis >10% NAFL-steatosis alone (bland steatosis) or steatosis without evidence of ballooning, with spotty inflammation of grade 1 maximum (2< foci/sox power field) and no fibrosis or fibrosis limited to mild periportal or perisinusoidal fibrosis (stage 1 or 2) NASH-steatosis (>5%) coexisting with hepatocellular ballooning and lobular necroinflammation, with or without fibrosis.
Prognostic variable(s)	Histological assessment of liver biopsy by one histopathologist, using the Kleiner-Brunt classification.
Confounders OR stratification strategy	univariate analysis of factors affecting fibrosis progression only.
Outcomes and effect sizes	Mean time between biopsies = 3.4 year (+/- 2.2), in 29% of people the biopsies were over 5 years apart • Fibrosis progression> 1 stage: 20 (29%) • Stable- 40 (42%) • Fibrosis regression- 20 (29%)
Comments	Low risk of bias. People who significantly lost weight during the follow up did not have a repeat biopsy.

Reference	Sorrentino 2010 [904]
Study type and analysis	Prospective observational study

Reference	Sorrentino 2010 [904]
Setting	Italy
Number of participants and characteristics	n= 276 (149 people had a repeat biopsy, 132 had biopsies suitable for assessment) Inclusions: obese people with NAFLD identified in a prior study, were no other causes of liver diseases identified. Exclusions: mean lifetime daily alcohol intake higher than 30 g/day for men and higher than 20 g/day for women. Cirrhosis on initial biopsy. nb. all people were referred to the nutritional department after the first biopsy, but no experimental pharmacological treatment for NAFLD was given. Mean age- 49.2 +/- 6.3 years Gender- 53 males: 79 females NAFLD-Steatosis with or without the features of steatohepatitis (inflammation and hepatocyte ballooning, with or without Mallory's hyaline or fibrosis). NAFL- steatosis +/-mild lobular inflammation NASH-steatosis + mild lobular inflammation and ballooning or subsinusoidal fibrosis
Prognostic variable(s)	Histological analysis of biopsy, analysed by a single pathologist, who was blinded to the patient details and the sequence of biopsies. All biopsies were 20 mm in length minimum. Fibrosis was classified using Brunt's criteria, with a significant change being defined as a progression or recession of >1 stage.
Confounders OR stratification strategy	Univariate and multivariate analysis for factors associated with fibrosis progression were undertaken using a backward elimination approach. Variables used included: sex age BMI at baseline biopsy basal HOMA-IR =(fasting serum insulin level mU/l x plasma glucose level mmol/l)/22.5) presence of Mallory's hyaline, hepatocyte ballooning Hypertension-defined as having diagnosed hypertension, or being on antihypertensive medication the grade of portal and lobular inflammation (grades 2 and 3 were combined) amount of fibronectin the grade of steatosis

Reference	Sorrentino 2010 [904]
	diagnosis of NASH at baseline
Outcomes and effect sizes	mean follow up time was 6.4 years (range 5-8.3 years) • fibrosis progression: 45 (34%) • stable: 76 (58%) • fibrosis regression: 11 (8%)
	Multivariate analysis of factors at baseline associated with fibrosis progression at baseline: lobular deposition of fibronectin >1, OR 14.1 (CI95% 6.9-32.3) p value <0.001 hypertension- OR 4.8 (CI95% 2.7-18.2) p=0.028 HOMA IR score>10, OR 1.9 (CI95% 1.6-121) p=0.004
Comments	High risk study. A large cohort although many lost to follow up and reasons for this not adequately reported.

Reference	Teli 1995 [956]
Study type and analysis	prospective observational study
Setting	UK
Number of participants and characteristics	n= 26 (12 people had repeat biopsies) Inclusion: People who had a principal histological diagnosis of fatty liver Exclusion: weekly consumption of ethanol >201g for men, >150g for women, or ethanol on detected on bloods, negative viral or autoimmune screens. People who had any fibrosis or steatohepatitis. Mean age: 55 (range 26-79) years Gender: 8 males: 18 female nb. all people were invited for repeat follow up, and if they had raised liver function tests or abnormal liver imaging were offered repeat liver biopsy. Recruited: from one hospitals database between 1978-1985
Prognostic variable(s)	Histological analysis of biopsy, analysed by a single pathologist.

Reference	Teli 1995 [956]
Confounders OR stratification strategy	No analysis on factors affecting fibrosis progression.
Outcomes and effect sizes	follow up time range 7.6-16 years • Progression to fibrosis- 1 (8%) • Stable (no fibrosis) - 11 (92%)
Comments	High risk of bias. Only those with deranged LFTs or imaging had further biopsy. High attrition rate.

Reference	Wong 2010[1034]
Study type and analysis	Prospective longitudinal study
Setting	China
Number of participants and characteristics	n= 54 (52 people had serial biopsies) Inclusions- aged >18 YO, biopsy proven NAFLD. Exclusion- >20g/day alcohol for me, and 10/g day of alcohol for women. People with any other serological of clinical reason for liver disease (for example, hepatitis, autoimmune and hepatotoxic drugs) Nb. People followed up every 6 months, with a dietary counselling session provided at baseline and encouraged to partake in physical activity >3 /week. Mean age- 47 +/- 9 years Gender- 34 male: 18 female NAFLD-histologic evidence of steatosis with or without the presence of necroinflammation and fibrosis, without known causes of fatty liver NAFL- steatosis without necroinflammation NASH- lobular inflammation, hepatocytes ballooning or intralobular hepatocyte necrosis +/- fibrosis.
Prognostic variable(s)	Histological assessment of liver biopsy, by two independent pathologists, who were blinded to the clinical and laboratory data. Assessed using the Brunt scale. length of biopsy was 18mm. Fibrosis progression was defined as >1 stage.
Confounders OR	univariate analysis with any factors found to be significant then put into a multivariate analysis

Reference	Wong 2010[1034]
stratification strategy	
Outcomes and effect sizes	mean follow up time was 36 months • Fibrosis progression 14 (27%) • Stable 25 (48%) • Fibrosis regression 13 (25%)
	Multivariate analysis (included BMI, waist circumference, ALT, low density lipoprotein-cholesterol level) Change in waist circumference : adjusted OR for each 1 cm increase, 1.3; 95%CI 1.1 to 1.5, p=0.002 High baseline low density lipoprotein- cholesterol- adjusted OR for 1 mmol/l increase 2.7 95%CI 1.2 to 6.1, p=0.019
Comments	Low risk of bias. Prospective designed study with low attrition rate. Good use of two pathologists and interrater reliability.

H.5 Extra-hepatic conditions

Reference	Bae 2011[99]
Study type and analysis	Retrospective cohort (medical record review) Cox proportional hazards analysis
Country and setting	Single healthcare centre, Korea
Duration of study	January 2005 to December 2009
Number of participants and characteristics	n = 7849 Inclusion criteria Individuals without diabetes at baseline who participated in comprehensive health check-ups annually for 5 years. Exclusion criteria Alcohol intake >20g/day, type 1 or 2 diabetes, positive serologic markers for hepatitis B or C virus, liver cirrhosis, or missing data (3101/10950) Population characteristics

Reference	Bae 2011[99]
	Mean age (SD): 44.5 (5.4) years Sex: 5409 men, 2440 women Mean BMI (SD): non NAFLD NFG 22.5 (2.4); NAFLD NFG 25.6 (2.4); non NAFLD IFG 23.6 (2.4); NAFLD IFG 26.1 (2.4) kg/m^2 Mean SBP (SD): non NAFLD NFG 109.6 (13.5); NAFLD NFG 115.8 (13.9); non NAFLD IFG 115.9 (15.2); NAFLD IFG 26.1 (2.4) mmHg HOMA-IR: non NAFLD NFG 1.7 (0.6); NAFLD NFG 2.28 (0.76); non NAFLD IFG 2.2 (0.76); NAFLD IFG 2.89 (1.05) IFG: 2049 (26%) NAFLD: 2292 (29%) NAFLD and IFG combinations: normal FG + no NAFLD 4353 (55.5%); normal FG + NAFLD 1447 (18.4%); impaired FG + no NAFLD 1204 (15.3%); impaired FG + NAFLD 845 (10.8%) Follow up Mean (SD) follow-up: 47.4 (5) months
Prognostic variable(s)	NAFLD diagnosed using abdominal ultrasound using 3.5 MHz probe. Criteria for NAFLD included hepatoreal echo contrast, liver brightness, deep attenuation, and vascular blurring. Several experienced radiologists performed ultrasound. Impaired fasting glucose (IFG) defined as fasting plasma glucose between 100-125 mg/dL.
Confounders	Age, sex, BMI, triglyceride, HDL cholesterol, systolic BP, smoking status, physical activity, alcohol intake, and coexisting IFG.
Outcomes and effect sizes	Development of diabetes defined as ≥126 mg/dL or A1C ≥6.5%. Also subjects who had a history of diabetes or currently used insulin or oral anti-diabetic drugs based on the self-report questionnaire at each visit were considered to have developed diabetes. 435 (5.5%) of total population progressed to diabetes; 9.9% NAFLD; 3.7% non-NAFLD • Subjects with NAFLD had an HR of 1.33 (95%CI 1.07-1.66) for the development of diabetes compared with the non-NAFLD groups (*p*=0.010) <u>Sub-group analyses</u> This paper also presented results for the two groups stratified by fasting glucose status. They found that the higher risk for diabetes only existed in the impaired fasting glucose group. Reference group = Non-NAFLD and normal fasting glucose. • NAFLD + normal fasting glucose: 1.39 (0.93-2.08) • Non-NAFLD + impaired fasting glucose: 6.79 (5.03-9.06) • NAFLD + impaired fasting glucose: 8.95 (6.49-12.35 A related paper printed on the same study population[204] presented results stratified by whether NAFLD was diagnosed by elevated liver enzymes

Reference	Bae 2011[99]
	(≥30 IU/L in men and 19 IU/L in women) or ultrasound or both. They found that the people who had NAFLD with both elevated ALT and ultrasound steatosis have increased risk for future diabetes development. Reference group = No NAFLD by both ALT and ultrasound. • NAFLD by increased ALT only: HR 1.20 (0.82-1.54) • NAFLD by ultrasound only: HR 1.03 (0.76-1.40) • NAFLD by increased ALT + ultrasound: 1.64 (1.27-2.13) A related paper on the same study population[932] with less predictors accounted for in the MVA found stronger associations: • Adjusted +baseline glucose OR: 2.05 (95% CI 1.35-3.12) for people with NAFLD compared to those without NAFLD. • Adjusted OR: 3.24 (95% CI 2.19-4.78) for people with NAFLD compared to those without NAFLD. A related paper on the same study population[929] (unclear baseline differences as presented differently) presented results stratified by fatty liver, insulin resistance and overweight/obesity. Reference group = No fatty liver, not obese, no insulin resistance. • Fatty liver alone: aOR 2.73 (1.38-5.41) • IR + fatty liver: aOR 6.73 (3.49-12.97) • Obese + fatty liver: aOR 3.23 (1.78-5.89) • Fatty liver + obese + IR: aOR 14.13 (8.99-22.2)
Comments	General limitations: Retrospective nature of the study design raises concerns about patient selection. No detailed description of patient selection re: consecutive or random, unsure why these people were having 'comprehensive health checks annually. No information of assessor variability for NAFLD diagnoses.

Reference	Chang 2008[189]
Study type and analysis	Prospective cohort Cox proportional hazards analysis
Country and setting	Single healthcare centre university hospital, Korea
Duration of study	Recruitment in 2002, followed-up in October 2006
Number of participants	n = 8329

Reference	Chang 2008[189]
and characteristics	Inclusion criteria All men working at one of the largest semiconductor manufacturing companies or its 13 affiliates, aged 30 to 59 years required to participate in comprehensive health checks. Non-diabetic and non-hypertensive Korean men. Exclusion criteria Anything that might influence kidney function of ultrasonography findings of the liver as a result of another liver disease: history of malignancy, history of cardiovascular disease, use of blood lipid-lowering agents, FBG ≥ 126 mg/dl, current use of blood-glucose lowering agents, taking medication for hypertension or had blood pressure of ≥140/90 mm Hg, antiviral drugs for chronic active hepatitis, positive serology for hepatitis B or C, history of known liver diseases, recent use of medication that could affect steatosis, abnormal ultrasound findings of chronic liver disease, liver cirrhosis, intrahepatic or extrahepatic cholelithiasis and abnormal dilation of biliary tree, medication for CKD, proteinuria, eGFR <60ml/min, alcohol intake ≥20 g/d, missing data. Population characteristics Mean age (95% CI): non NAFLD 36.6 (36.5-36.7); NAFLD 37 (36.8-37.2) years All male cohort Mean BMI (95% CI): non NAFLD 23 (22.9-23); NAFLD 25.7 (25.6-25.8) kg/m^2 Mean SBP (95% CI): non NAFLD 111.9 (111.7-112.1); NAFLD 112.1 (111.7-112.5) mmHg Mean DBP (95% CI): non NAFLD 71.9 (71.7-72.1); NAFLD 72.2 (71.9-72.5) mmHg Metabolic syndrome: non NAFLD 5.1%; NAFLD 9.7% (p <0.001) – not adjusted for in MVA (not significant at univariate level) NAFLD: 30.2% at baseline. Follow-up 1054/9383 no follow-up examinations. Mean follow-up period (SD): 3.21 (1.01) years.
Prognostic variable(s)	Fatty liver based on abdominal ultrasound (3.5 MHz transducer) carried out by three radiologists unaware of laboratory values. Four criteria – hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring. Diagnosis made by presence of hepatorenal contrast and liver brightness. Performed by three experienced radiologists.
Confounders	Age, NAFLD, obesity (BMI ≥25 kg/m^2), eGFR, low HDL-C (<40 mg/dL), high triglycerides (≥150 mg/dL), incident hypertension.
Outcomes and effect sizes	Development of CKD defined as either proteinuria or eGFR <60 mL/min per 1.72 m^2 324 (3.9%) new cases of CKD, no details reported on NAFLD and CKD status • Adjusted RR 1.44 (95% CI 1.12-1.84) for men with NAFLD compared to men without NAFLD developing CKD.

Reference	Chang 2008[189]
Comments	General limitations: seems to be a consecutive sample. Unclear how much attrition based on NAFLD status. No reporting or adjusting for inter-rater variability.

Reference	Chang 2013[187]
Study type and analysis	Prospective cohort Cox proportional hazards analysis
Country and setting	Single healthcare centre, Korea
Duration of study	Original health check-up 2005-2006, followed-up to December 2011
Number of participants and characteristics	n = 38, 291 Inclusion criteria Corporate health examination database followed annually or biennially. Exclusion criteria Missing ultrasonography or other covariates at baseline, history of malignancy, known liver disease or using medications for liver disease, history of cirrhosis or finding on ultrasound, alcohol intake ≥30 g/day for men and ≥20 g/day for women, positive serological markers for hepatitis B or C virus, and use of medications associated with NAFLD within the past year. Further exclusions of DM at baseline and not attending follow-up (4875/47834) – on average these people were younger and had more favourable metabolic profiles than the remaining included people. Population characteristics Mean age (SD): no NAFLD 36.5 (4.4); NAFLD low NFS 37.3 (4.5); NAFLD int/high NFS 41.9 (5) years Sex (% Male): no NAFLD 54.2%; NAFLD low NFS 89.8%; NAFLD int/high NFS 90.9% Mean BMI (SD): no NAFLD 22.3 (2.6); NAFLD low NFS 26 (2.6); NAFLD int/high NFS 27.6 (2.9) kg/m^2 Mean SBP (SD): no NAFLD 110.2 (12.3); NAFLD low NFS 117.6 (12.9); NAFLD int/high NFS 121.1 (15.6) mmHg Mean DBP (SD): no NAFLD 70.7 (8.8); NAFLD low NFS 76.5 (9.1); NAFLD int/high NFS 80.1 (11.3) mmHg Metabolic syndrome: no NAFLD 5.4%; NAFLD low NFS 33.2%; NAFLD int/high NFS 73.7% Hypertension: no NAFLD 5.9%; NAFLD low NFS 15.7%; NAFLD int/high NFS 31.5%

Reference	Chang 2013[187]
	NAFLD (at baseline): Any NAFLD 30%; NAFLD and low NFS 29%; NAFLD and intermediate or high NFS 1% Development of NAFLD in those without NAFLD at baseline: 20% developed NAFLD with low NFS, 2% developed NAFLD with intermediate NFS. Follow-up Average follow-up period for those who did not develop diabetes mellitus was 5.1 years.
Prognostic variable(s)	Ultrasonographic diagnosis of fatty liver defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma. Inter-observer reliability and intra-observer reliability were substantial (0.74) and excellent (0.96). NAFLD defined as the presence of fatty liver in the absence of excessive alcohol use (<20g/d for women and <30g/d for men) or other identifiable causes. NAFLD fibrosis score (NFS) categorised people into three groups: high probability for advanced fibrosis (>0.676), intermediate probability (0.676 to -1.455) and low probability (< -1.455). Very few subjects identified as high probability so for analysis this group was combined with the intermediate risk group.
Confounders	Age, BMI, sex, smoking, alcohol intake, exercise, family history of diabetes mellitus (DM) and other metabolic markers including total cholesterol, triglycerides, HDL-cholesterol, HOMA-IR and hsCRP.
Outcomes and effect sizes	Development of diabetes defined as ≥126 mg/dL or A1C ≥6.5% or use of blood glucose-lowering agents. 2025 (5%) of total population progressed to diabetes; no details provided for number in each NAFLD status group. • Subjects with NAFLD and low NFS had an HR of 1.81 (95%CI 1.61-2.04) for the development of diabetes compared with the non-NAFLD group (p<0.001) • Subjects with NAFLD and intermediate or high NFS had an HR of 3.84 (95%CI 2.93-5.02) for the development of diabetes compared with the non-NAFLD group (p<0.001) • Subjects with NAFLD and intermediate or high NFS had an HR of 2.38 (95%CI 1.84-3.04) for the development of diabetes compared with the NAFLD and low NFS group (p NR)
Comments	General limitations: No detailed description of patient selection re: consecutive or random. No clear details on over numbers of NAFLD patients and diabetes patients in cohort at follow-up.

Reference	El Azeem 2013[275]
Study type and analysis	Prospective cohort Logistic regression analysis
Country and setting	Multicentre, Egypt and Saudi Arabia

Reference	El Azeem 2013[275]
Duration of study	Enrolled between Jan 2009 and Feb 2010, followed-up every 6-12 months for three years
Number of participants and characteristics	n = 747 Inclusion criteria Normal or near normal liver and kidney functions. Exclusion criteria Overt proteinuria or eGFR <60 ml/min/1.73 m^2 or receiving medical treatment for current kidney disease at the time of examinations. History of cardiovascular events (unstable angina, myocardial infarction, coronary revascularization, ischemic stroke, cerebral haemorrhage). Known history of liver disease including viral, genetic, autoimmune, and drug-induced liver disease or those with positive test for hepatitis B antigen or hepatitis C antibody. History of alcohol intake or cancer. Population characteristics Mean age (SD): NAFLD 52.10 (12.46); no-NAFLD 51.11 (10) years Sex: NAFLD 49.6%; no-NAFLD 48.6% male Mean BMI (SD): NAFLD 33.37 (5.11); no-NAFLD 34.35 (3.8) kg/m^2 Diabetes: NAFLD 79.4%; no-NAFLD 45.5% Mean SBP (SD): NAFLD 131.61 (14.83); no-NAFLD 136.61 (14.62) mmHg Mean DBP (SD): NAFLD 82.74 (8.11); no-NAFLD 84.50 (8.35) mmHg Metabolic syndrome: NAFLD 79.1%; no-NAFLD 61.4% NAFLD: 268 (35.8%) Follow up 403/1150 did not complete follow-up. According to baseline details these people did not differ significantly from those who completed the study.
Prognostic variable(s)	Radiological examination to diagnose fatty liver (operator blind to participant's clinical and lab findings) using four criteria – hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring.
Confounders	Age, gender, weight, BMI, waist circumference, smoking status, systolic BP, diastolic BP, antihypertensive, fasting blood glucose, HbA1c, duration of diabetes mellitus, oral hypoglycaemia, insulin therapy, total cholesterol, HDL-C, LDL-C, triglyceride, ALT, AST, metabolic syndrome (presence and mean score).
Outcomes and	Cardiovascular events defined as CHD, ischemic stroke and cerebral haemorrhage. CHD included UA, acute MI, silent MI, and coronary

Reference	El Azeem 2013[275]
effect sizes	revascularization. Cardiovascular events 246 (35.8%) overall; NAFLD 136 (50.7%); no-NAFLD 110 (23%). • Exp (beta) to odds ratio 5.210 (95% CI 1.93-4.25) for those with NAFLD developing cardiovascular events compared to no-NAFLD (p < 0.001). NAFLD the best predictor for cardiovascular impairment as indicated by the highest Exp to odds ratio.
Comments	General limitations: No detailed description of patient selection re: consecutive or random, unclear what type of patients these people were at original recruitment. No information provided on observer number or reliability. Unclear analysis reporting for inclusions in MVA.

Reference	Huang 2013[437]
Study type and analysis	Retrospective cohort Logistic regression analysis
Country and setting	Single centre, urban veterans hospital, Taiwan
Duration of study	January 2003 to 31 December 2010
Number of participants and characteristics	n = 1522 Inclusion criteria Health check with an initial negative colonoscopy and second colonoscopy Exclusion criteria History of colorectal cancer or colorectal adenoma, alcohol consumption >20 g/day 321/2289 excluded for incomplete data; 446/2289 excluded for initial polyp positive Population characteristics (presented stratified by outcome only) Mean age (SD): Non-adenoma group 53.3 (9.8); adenoma group 56.1 (9.0) years Gender: Non-adenoma group 57.7% male; adenoma group 72.7% male Mean BMI (SD): Non-adenoma group 23.7 (3.2); adenoma group 24.8 (3.1) kg/m^2 Metabolic syndrome: Non-adenoma group 15%; adenoma group 27.8% Diabetes: Non-adenoma group 5.3%; adenoma group 12% Hypertension: Non-adenoma group 19.5%; adenoma group 39.8%

Reference	Huang 2013[437]
	NAFLD: 40.7% of follow-up population had NAFLD at baseline Follow up Mean (SD): 2.59 (1.24) years
Prognostic variable	NAFLD based ultrasound performed at time of initial colonoscopy by an experienced radiologist. NAFLD diagnosed when fatty liver was present in the absence of viral (hepatitis B or C), autoimmune or other liver disease, or heavy alcohol consumption (>20 g/day).
Confounders	Age, BMI, gender, NAFLD, smoking, hypertension diabetes mellitus, metabolic syndrome.
Outcomes and effect sizes	Development of colorectal adenoma found during colonoscopy where size, number and location of polyps was recorded. 216 (14.2%) developed adenoma; 19.3% of NAFLD population; 10.6% of non-NAFLD population. 55.6% of those who developed adenoma had NAFLD at baseline; 38.8% of those who remained adenoma free had NAFLD at baseline. • Adjusted OR 1.45 (95% CI 1.07-1.98) for people with NAFLD developing colorectal adenoma after a negative baseline colonoscopy compared to people without NAFLD (p = 0.016) <u>Sub-group analysis</u> Risk of adenoma development in people with NAFLD with and without other comorbidities. Risk of adenoma was higher when NAFLD coexisted with other comorbidities • Adjusted OR 2.85 (95% CI 1.91-4.25) for people with NAFLD and metabolic syndrome compared with people without NAFLD and metabolic syndrome [adjusting for age, sex and smoking]. • Adjusted OR 4.30 (95% CI 2.72-5.98) for people with NAFLD and hypertension compared with people without NAFLD and hypertension [adjusting for age, sex and smoking].
Comments	General limitations: Presume consecutive but unclear how patients recruited. Unclear reliability for observations of NAFLD status. No attrition data reported.

Reference	Imamura 2014 [450]
Study type and analysis	Retrospective cohort Logistic regression analysis
Country and setting	Single medical healthcare centre, Japan
Duration of study	2006 to 2011

Reference	Imamura 2014 [450]
Number of participants and characteristics	n = 4842 Inclusion criteria Japanese participants aged 30-70 who received regular health check-ups in 1991, 1996, 2001, 2006, or 2011. For the current analysis only those who had participated in both 2006 and 2011 were analysed Exclusion criteria None reported. Population characteristics: Only available for all people in 2011 – not specified for those included in the 2006-2011 analysis Mean age (SD): Men 54.3 (10.7); women 55.8 (10.9) years Mean BMI (SD): Men 23.8 (3.2); Women 22.6 (3.5) kg/m^2 Hypertension: Men 44.6 %; Women 31.9% Dyslipidaemia: Men 50.7%; Women 39.6% Fatty liver 2011: Men 38%; Women 20.9% Gender (current analysis): Male 3351; Female 1967 No diabetes at baseline: 4842/5318 Follow up No follow up information. Only used those who had data available both years.
Prognostic variable	Fatty liver using ultrasound based on the presence of a bright liver (increased echogenicity) with liver-kidney contrast (increased echogenicity of the liver compared to the right kidney)
Confounders	Age, BMI, Hypertension, Dyslipidaemia, fatty liver. Results stratified by gender.
Outcomes and effect sizes	Diabetes at study finish (2011) defined by the use of medicaltion for diabetes mellitus, fasting blood glucose ≥126 mg/dl, or HbA1c ≥6.5% 631 (13%) developed diabetes. Results presented for the limited subjects who were HBs-antigen negative, HCV-antibody negative, and not on medication for hypertension and dyslipidaemia n=3545/4842 • Adjusted OR 1.76 (95% CI 1.11-2.80) for men with fatty liver developing diabetes compared to those without fatty liver

Reference	Imamura 2014 [450]
	• Adjusted OR 1.84 (95% CI 0.85-4.22) for women with fatty liver developing diabetes compared to those without fatty liver
Comments	General limitations: Unclear how patients recruited. No attrition data reported due to retrospective nature of study design. No exclusion criteria listed.

Reference	Jenks 2014[465]
Study type and analysis	Prospective cohort Linear regression analysis
Country and setting	Scotland
Duration of study	Recruitment between 2006-2007 for Type 2 diabetes study, follow-up clinic at one year to assess liver function and structure (alcohol intake and obtain ultrasound), final follow-up three years later
Number of participants and characteristics	n = 601 Inclusion criteria Type 2 diabetes aged 60-74 picked randomly from diabetes register of those attending both hospital diabetes clinics and those managed solely in primary care. Subgroup of original 933 patients after excluding those who had baseline evidence of CKD (defined as the presence of albuminuria or an eGFR <60 ml/min 1.73m^2 at baseline. Exclusion criteria None reported. Population characteristics: (based on original baseline group of 933 participants) Mean age (SD): 67.8 (4.2) years Male 52% (based on sub-group of those without a secondary cause for chronic liver disease) NAFLD 59% Mean BMI (SD): NAFLD 32.5 (5.7); no-NAFLD 30.4 (5.7) kg/m^2 Mean duration of diabetes (SD): NAFLD 7.3 (5.3); no-NAFLD 9.0 (7.2) years

Reference	Jenks 2014[465]
	Mean SBP (SD): NAFLD 133 (16); no-NAFLD 134 (18) mmHg Mean DBP (SD): NAFLD 69 (9); no-NAFLD 69 (8.9) mmHg Follow-up 133 did not attend one year clinic and 113 did not attend the follow up clinic.
Prognostic variable(s)	NAFLD defined as the presence of grade 3 (severe steatosis) hepatic steatosis on ultrasound in the absence of secondary cause (viral hepatitis, autoimmune liver disease, hepatoxic medications or alcohol excess defined as a current alcohol intake ≥ 14 units/week or history of alcohol excess).
Confounders	Age, sex BMI, duration of diabetes, HbA1c and systolic blood pressure
Outcomes and effect sizes	Development of CKD during follow up defined as albuminuria or an eGFR <60 ml/min 1.73m^2 110 (18.3%) developed CKD. 20.2% of those who developed CKD had NAFLD, 19.5% did not. • Adjusted RR 1.01 (95% CI 0.49-2.09) for developing CKD for people with NAFLD compared to those without NAFLD (p = 0.98)
Comments	General limitations: Participants were included at random from the database, although no information is provided on how this random inclusion was conducted. Unclear how attrition was distributed between NAFLD groups based on first and second follow-up. Unclear outcome reporting with respect to specific confounders entered into MVA.

Reference	Kasturiratne 2013 [497]
Study type and analysis	Prospective cohort Cox proportional hazards analysis
Country and setting	Single health centre, Sri Lanka
Duration of study	Screening tests carried between January to September 2007 and followed up for 3 years
Number of participants and characteristics	n = 1857 Inclusion criteria Ragama Health Study cohort aged between 35 to 64 years, selected using age stratified random sampling from the electoral lists, screened using structured interview, liver ultrasound, biochemical and serological tests, negative for hepatitis B and C serological markers and anti-hepatitis C virus.

Reference	Kasturiratne 2013 [497]
	Exclusion criteria Diabetes at baseline Population characteristics Age, mean (SD): with NAFLD 52.9 (7.2), without NAFLD 52.3 (8.0) years BMI, mean (SD): with NAFLD 27.1 (3.8), without NAFLD 22.6 (3.5) mg/m^2 Males: NAFLD 33.2%, no NAFLD 48% Hypertension: NAFLD 56.9%, no NAFLD 38.8% Dyslipidemia: NAFLD 56.5%, no NAFLD 49.6% IFG: NAFLD 66.9%, no NAFLD 51.9% NAFLD at baseline: 926 (32%) NAFLD at follow up: 543 (29%) Follow up 362/2276 were not re-assessed at follow-up. 15 participants with NAFLD at baseline had started consuming alcohol above the weekly safe limit over the three years since diagnosis.
Prognostic variable(s)	NAFLD was diagnosed based on the presence of fatty liver according to ultrasound and alcohol consumption below the safe limit (Asian standard: 14 units for men and 7 units for women). Ultrasound (8MHz probe) performed by three doctors with special training in ultrasonography. Ultrasound criteria for fatty liver had to include three of the following: increased echogenicity of the liver compared to the kidney and spleen, obliteration of the vascular architecture of the liver and deep attenuation of the ultrasonic signal.
Confounders	Sex, age, baseline BMI, waist circumference, presence of hypertension, dyslipidaemia, elevated ALT at baseline and family history of diabetes.
Outcomes and effect sizes	Diabetes was defined as fasting blood sugar >6.9 mmol/L. Incidence of diabetes at 3 years 104/528 (20%) people with NAFLD; 138/1314 (10.5%) people without NAFLD • HR (95% CI): 1.64 (1.2-2.23) for people with NAFLD developing diabetes compared to those without NAFLD.
Comments	General limitations: No detailed description of patient selection re: consecutive or random, no information of assessor reliability for NAFLD status. Unclear outcome reporting concerning attrition and inclusion in MVA.

Reference	Kim 2008 [508]
Study type and	Retrospective cohort

Reference	Kim 2008 [508]
analysis	Logistic regression analysis
Country and setting	Single health promotion centre, Korea
Duration of study	Retrospectively examining the clinical and laboratory data of subjects in 2000 and their 5 year follow-up in 2005
Number of participants and characteristics	n = 6096 Inclusion criteria Patients who attended the Asan Medical Centre for medical check-ups in 2000 and returned 5 years later for follow-up examinations. Exclusion criteria Patients with diabetes at baseline, those positive for hepatitis B virus surface antigens or HCV antibody, those with hepatic enzyme (ALT/AST) concentrations higher than three times the normal limit and patients with ultrasonographic evidence of liver cirrhosis or suspicion of malignancy. Population characteristics for subjects with no fatty liver, mild fatty liver and moderate to severe: Male (%): 61.9, 79.6, 85.9 BMI (kg/m^2): 22.9 (2.5), 25.2 (2.2), 26.4 (2.4) Systolic BP (mmHg): 119 (16), 124 (15), 128 (16) Diastolic BP (mmHg): 78 (11), 81 (11), 83 (11) Follow up No attrition information provided.
Prognostic variable(s)	NAFLD severity was assessed using abdominal ultrasound by six radiologists. Severity of fatty infiltration graded as mild defined as slight diffuse increase in the fine echoes in the hepatic parenchyma with normal visualisation of the diaphragm and intrahepatic vessel borders; moderate defined as moderately diffuse increase in the fine echoes with slightly impaired visualisation of the diaphragm and intrahepatic vessels; or severe defined as marked increase in the fine echoes with poor or no visualisation of the diaphragm, intrahepatic vessels and posterior portion of the right lobe of the liver. Only moderate to severe included in this review.

Reference	Kim 2008 [508]
Confounders	Age, sex, family history of diabetes, smoking, blood pressure, fasting glucose, BMI, ALT levels, high-density lipoprotein cholesterol, triglyceride levels and different ultrasonographer.
Outcomes and effect sizes	Diabetes was measured using fasting blood samples for plasma glucose. Diagnosed based on clinical history or use of glucose-lowering medications or FPB ≥7.0 mmol/l. Incidence of diabetes at 5 years: 234 (4.3%) of total population. 153/1790 (8.5%) of people with fatty liver developed diabetes. 81/3582 (2.3%) of people without fatty liver developed diabtes. • Adjusted RR 2.29 (95% CI 1.13-4.63) for people with moderate to severe fatty liver versus no fatty liver developing diabetes. <u>Outcomes not included in this review</u> • Adjusted RR 1.49 (05% CI 0.82-2.71) for mild fatty liver versus no fatty liver
Comments	General limitations: No detailed description of patient selection re: consecutive or random, no information of assessor blinding for NAFLD status or diabetes outcome. Although frequent alcohol drinkers were excluded from multivariate analysis model, there is no definition of the level of alcohol consumed by the people included. No attrition information provided; retrospective nature of study design raises concerns about patient selection.

Reference	Lau 2010[557]
Study type and analysis	Prospective cohort Linear and logistic regression analyses
Country and setting	Germany
Duration of study	Baseline examinations between 1997 and 2001. Follow-up between 2002 and 2006.
Number of participants and characteristics	n = 2417 Inclusion criteria Participants drawn from population registries who were German citizens whose main residency was in the study area were eligible. Exclusion criteria

Reference	Lau 2010[557]
	Uncertain diagnosis of fatty liver, positive for hepatitis B surface antigen, positive for hepatitis C virus antibody, known history of cirrhosis, missing BP measurement and missing ALT data. Population characteristics Mean age (SD): US-/ALT- 47.5 (15.7); US-/ALT+ 42.1 (13.8); US+/ALT- 59.8 (11.9); US+/ALT+ 51.9 (12.4) years Sex (% Male): US-/ALT- 35.6%; US-/ALT+ 76%; US+/ALT- 48.5%; US+/ALT+ 77.7% Mean BMI (SD): US-/ALT- 25.8 (4.3); US-/ALT+ 27.2 (3.8); US+/ALT- 29.6 (4.6); US+/ALT+ 30.7 (4.3) kg/m^2 Mean alcohol consumption (SD): US-/ALT- 11 (17); US-/ALT+ 18.9 (39.5); US+/ALT- 13.5 (24.7); US+/ALT+ 21.5 (26.3) g/day Diabetes: US-/ALT- 3.5%; US-/ALT+ 3.5%; US+/ALT- 17.8%; US+/ALT+ 14% Follow-up Conducted on average 5.3 years after baseline. 109/3300 excluded at follow-up for the reasons listed in exclusion criteria. 774/3300 excluded as using anti-hypertensive medication at baseline.
Prognostic variable(s)	Fatty liver disease defined by the presence of a hyper-echogenic liver pattern, with evident density differences between hepatic and renal parenchyma together with increased serum ALT levels (>75^{th} percentile) using four categories: 1) US negative/ALT negative, 2) US negative/ALT positive, 3) US positive/ALT negative, 4) US positive/ALT positive.
Confounders	Age, sex, waist circumference, BMI, diabetes mellitus, average daily alcohol consumption and the use of antihypertensive medication.
Outcomes and effect sizes	Hypertension was defined as increased SBP (≥140 mmHg) and DBP (≥90 mmHg) or use of antihypertensive medication. No raw data reported on number of those who developed hypertension during the study. • Adjusted OR 1.7 (95% CI 1.2-2.3) for those with US positive for fatty liver and increased ALT compared to those US negative and ALT negative. Other groups: • Adjusted OR 1.1 (95% CI 0.8-1.6) for those with US positive for fatty liver without increase ALT compared to those US negative and ALT negative. • Adjusted OR 1.3 (95% CI 0.9-1.8) for those with US negative for fatty liver but increased ALT compared to those US negative and ALT negative. Interaction analyses to investigate whether alcohol consumption modifies the association between fatty liver disease and hypertension did not obtain statistical significance so no analyses were stratified by alcohol consumption.
Comments	General limitations: Population did include those who had the outcome at baseline. However they provide separate analyses excluding those on

Reference	Lau 2010[557]
	anti-hypertensive medication. Unclear attrition differential between groups as not reported. No information on NAFLD rater reliability.

Reference	Lazo 2011[564,564]
Study type and analysis	Prospective cohort Cox proportional hazards regression analysis
Country and setting	USA
Duration of study	Patients recruited between 1988-1994. Followed until death or 31 December 2006
Number of participants and characteristics	n = 11269 Inclusion criteria All participants aged ≥20 years for the Third National Health and Nutrition Examination Study and Mortality follow-up study. Exclusion criteria 102/11371 excluded in sensitivity analyses based on exclusion of those with prevalent CVD, prevalent cancer, hepatitis B and C or elevated alcohol consumption or using anti-retrovirals. Population characteristics Mean age (SE): No NAFLD 41.4 (0.4); NAFLD 48.3 (0.6); NASH 42.9 (1.2) years Men: No NAFLD 45.6%; NAFLD 52.4%; NASH 54.1% BMI ≥35: No NAFLD 5%; NAFLD 19%; NASH 33.5% Diabetes: No NAFLD 5.4%; NAFLD 15.8%; NASH 21.3% Hypertension: No NAFLD 19.7%; NAFLD 35.7%; NASH 38.4% NAFLD 17% NASH 4% Follow-up Median Follow-up 14.5 years (maximum 18 years).
Prognostic	NAFLD as the presence of moderate to severe hepatic steatosis based on ultrasound with normal liver enzymes.

Reference	Lazo 2011[564,564]
variable(s)	NASH as the presence of moderate to severe hepatic steatosis based on ultrasound with increased levels of liver enzymes in the absence of antibodies for hepatitis B and hepatitis C and without evidence of iron overload. Ultrasound (3.57 and 5.0 MHz transducer) information on the presence of liver to kidney contrast, degree of brightness of the liver parenchyma, presence of deep beam attenuation, presence of echogenic walls in the small intrahepatic vessels, and definition of the gallbladder walls.
Confounders	Sex, age, race or ethnicity, smoking status, BMI, education, alcohol consumption, physical activity, hypertension, diabetes and raised GGT levels
Outcomes and effect sizes	Cardiovascular disease mortality defined as deaths with underlying cause of deaths codes of ICD-10 I00-I69 using the Underlying Cause of Death-113 groups (international classification of disease, 10th edition, developed by the National Centre for Health Statistics). These include Acute rheumatic fever and chronic rheumatic heart diseases; Hypertensive heart disease; Hypertensive heart and renal disease; Acute myocardial infarction; Other acute ischemic heart diseases; Atherosclerotic cardiovascular disease, so described; All other forms of chronic ischemic heart disease; Acute and subacute endocarditis; Diseases of pericardium and acute myocarditis; Heart failure; All other forms of heart disease; Essential (primary) hypertension and hypertensive renal disease; Cerebrovascular diseases. 706 (6%) died of cardiovascular disease related events during follow-up; 9% of the NAFLD group; 4% of NASH group; 6% of non-NAFLD group. • Adjusted HR 0.86 (0.67-1.11) for those with NAFLD dying of CVD related events compared to those without NAFLD • Adjusted HR 0.59 (0.29-1.20) for those with NASH dying of CVD related events compared to those without NASH
Comments	General limitations: Unclear how patients were identified and included in the study. Unclear attrition between prognostic risk factor groups.

Reference	Lee 2012[579]
Study type and analysis	Retrospective cohort Cox proportional hazards analysis
Country and setting	Korea, medical insurance claims database.
Duration of study	Baseline between July 2002 and June 2006. Follow-up December 2008.
Number of participants and characteristics	n = 5517 Inclusion criteria Women aged 35-80 years who underwent life insurance company health examinations Exclusion criteria

Reference	Lee 2012[579]
	NR Population characteristics Mean age (SD): NAFLD 50 (7.7); no-NAFLD 46.2 (6.4) years Mean BMI (SD): NAFLD 26.1 (3.1); no-NAFLD 22.2 (2.6) kg/m^2 Mean SBP (SD): NAFLD 115.2 (14.8); no-NAFLD 106.9 (13) mmHg MEAN DSP (SD): NAFLD 76.1 (9.7); no-NAFLD 70.9 (8.4) mmHg Hypertension 8.1% Diabetes 2.6% NAFLD 15.1% Follow up Up to seven years. No data reported on mean follow-up time. No attrition details provided.
Prognostic variable(s)	NAFLD based on abdominal ultrasound (3.5 MHz transducer) by several experienced radiologists. NAFLD diagnosed if, of the four known ultrasound criteria (hepatorenal echo contrast, liver brightness, deep attenuation and vascular blurring), they showed hepatorenal contrast and bright liver.
Confounders	Age, BMI, blood pressure, fasting glucose, total cholesterol, triglycerides, HDL-cholesterol, NAFLD, smoking habits, and cardiometabolic risk factors.
Outcomes and effect sizes	Colorectal neoplasm information obtained through medical certificate codes for insurance claims. Obtained using the ICD-10 based on diagnosis by colonoscopic examinations and biopsies. Colorectal neoplasms included those due to adenomatous polyps of the colon, carcinoma in situ of the colon, rectosigmoid junction, and rectum, and malignant neoplasms in the colon, rectosigmoid junction and the rectum. 15 (0.27%) women developed colorectal cancer. • Adjusted RR 3.08 (95% CI 1.02-9.34) for women with NAFLD developing colorectal cancer compared to women without NAFLD.
Comments	General limitations: unclear how they ascertain that the fatty liver population is NAFLD specifically. While they mention that alcohol drinking habits were assessed at baseline, this is not listed as exclusion criteria, and drinking habits are not included in the MVA. Unclear control for rater differences in NAFLD diagnosis by ultrasound. Unclear definition of NAFLD. No attrition information reported. Less than 10 outcome events per variable make the analysis unstable and suggest a concern with the results.

Reference	Morling 2015 [671]

Reference	Morling 2015 [671]
Study type and analysis	Retrospective cohort Cox proportional hazards analysis
Country and setting	Scotland, Diabetes Register
Duration of study	Baseline unclear (reported elsewhere). Follow-up August 2011
Number of participants and characteristics	n = 663 Inclusion criteria Type 2 diabetes aged 60-75 years living in Lothian, Scotland, UK. Exclusion criteria NR Population characteristics (for total population only – including those with baseline CVD n=1,033) Mean age (SD): 67.9 (4.2) years Gender: 61.2% male Mean BMI (SD): 31.3 (5.6) kg/m^2 Mean SBP (SD): 133.2 (16.4) mmHg Mean DSP (SD): 69.1 (9)) mmHg Median duration of diabetes (IQR): 6 (3-11) years Follow up Mean 4.4 years. Unclear attrition as unclear reporting of those who had measurements of both and no CVD at baseline.
Prognostic variable(s)	NAFLD defined as the presence of steatosis on ultrasound scan, without alcohol excess or use of hepatotoxic mediation and a negative liver screen.
Confounders	Age, sex, duration of diabetes, treatment of diabetes, lipid-lowering drugs, blood pressure-lowering drugs, depravation, smoking status, excess alcohol consumption, BMI, systolic BP, diastolic BP, HbA1c, HDL-cholesterol, total cholesterol and eGFR.
Outcomes and effect sizes	Incident cardiovascular disease using ICD-10 (and related ICD-9) codes. Included myocardial infarction, angina, stroke, transient ischaemic attack, coronary intervention, intermittent claudication, peripheral vascular intervention, and carotid endarterectomy occurring between baseline/year 1 and end of August 2011, for both fatal and non-fatal events in those patients without prevalent CVD at baseline.

Reference	Morling 2015 [671]
	44/663 (6.6%) people with incident CVD • Adjusted HR 0.90 (95% CI 0.40-2.00) for people with diabetes and steatosis developing incident cardiovascular disease compared to those people with diabetes without steatosis (*p*=0.787)
Comments	General limitations: Unclear whether prognostic variable in the report it full definition of NAFLD or steatosis. Unclear attrition. Unclear NAFLD status at baseline and follow-up (not reported). No detailed information of assessor definitions for steatosis status or inter- and intra-observer variability.

Reference	Park 2013[747]
Study type and analysis	Prospective cohort study Cox proportional hazards modelling
Country and setting	Single health centre, Korea
Duration of study	Medical check-up in 2005. Follow-up visit between 2006-2010.
Number of participants and characteristics	n = 25232 Inclusion criteria Korean men who had been examined with abdominal ultrasonography and were categorised for NAFLD as either normal, mild or moderate to severe. Exclusion criteria Past history of malignancy, cardiovascular disease, receiving medication for lipid-lowering agents, alcohol intake of ≥20 g/day, elevated GGT levels (>100 U/L), elevated ALT levels (>100 U/L), positive serological marker for hepatitis B surface antigen and hepatitis C virus antibody, abnormal liver ultrasound findings of chronic liver disease, liver cirrhosis, and/or current past history of clonorchiasis (in 2005) and baseline of type 2 diabetes. Population characteristics for normal, mild and moderate to severe levels of NAFLD respectively. Mean (SD): Age (years): 42.4 (7.3), 42.7 (6.9), 41.2 (6.1) BMI (kg/m^2): 23.3 (2.4), 25.7 (2.3), 27.6 (2.7) Systolic BP (mmHg): 112.9 (13.6), 116.3 (14), 120.7 (14.9)

Reference	Park 2013[747]
	Diastolic BP (mmHg): 75.9 (9.1), 78.8 (9.6), 80.4 (10.3) Metabolic syndrome (%): 6.8, 26.1, 45.6 Follow up Average follow-up was 3.77 (SD 1.38) years.
Prognostic variable(s)	Presence and degree of fatty liver defined as abnormal hepatic features see on abdominal ultrasound. No definition of mild vs. moderate to severe supplied by the paper. Only moderate to severe group included in this review as the committee agreed that ultrasound is not sufficient to grade severity of NAFLD.
Confounders	Age, waist circumference, HDL-cholesterol, triglycerides, systolic BP, log(hsCRP), log(HOMA-IR), serum creatinine, family history of diabetes, regular exercise and metabolic syndrome (male only cohort).
Outcomes and effect sizes	Type 2 diabetes was defined as fasting serum glucose >126 mg/dL or haemoglobin A1c (HbA1c) ≥6.5%. Incidence of diabetes at 5 years: 2103 (8.4%) of total population. 1146/16374 (7%) of men with no fatty liver developed T2D; 755/7709 (9.8%) of men with mild fatty liver developed T2D; 204/1149 (17.8%) of men with moderate to severe NAFLD developed T2D. • HR 1.73 (95% CI 1.00-3.01) for men with moderate to severe fatty liver compared to without fatty liver. <u>Outcomes not included in this review</u> • HR 1.09 (95% CI 0.81-1.48) for men with mild NAFLD compared to men without NAFLD.
Comments	General limitations: No detailed description of patient selection re: consecutive or random, no detailed information of assessor definitions for NAFLD status or inter- and intra-observer variability. BMI not included in MVA. But waist circumference is (proxy).

Reference	Perazzo 2014[756,756]
Study type and analysis	Retrospective cohort Cox proportional hazards analysis
Country and setting	Institute of Carbometabolism and Nutrition, single hospital, France.
Duration of study	Patients recruited January 1999. Follow-up December 2012
Number of participants and characteristics	n = 2312 Inclusion criteria

Reference	Perazzo 2014[756,756]
	Two cohorts of patients – either those diagnosed with dyslipidaemia (LDL-cholesterol >160 mg/dL o triglycerides >150 mg/dL) or those with Type 2 diabetes (fasting glucose ≥126 mg/dL or 2-hour post-prandial glucose ≥200 mg/dL). Exclusion criteria Liver disease other than NAFLD (alcoholic cirrhosis, chorinc hepatitis B or C), absence of follow-up or missing data. Population characteristics (according to baseline fibrosis stage) Mean age (SD): No adv fibrosis 55 (12); adv fibrosis 62 (11) years Men: no adv fibrosis 50%; adv fibrosis 82% Mean BMI (SD): no adv fibrosis 27.1 (5.3); adv fibrosis 28.5 (4.8) Mean systolic BP (SD): no adv fibrosis 130 (16); adv fibrosis 133 (16) Mean diastolic BP (SD): no adv fibrosis 77 (10); adv fibrosis 76 (12) Hypertension: no adv fibrosis 55%; adv fibrosis 75% Metabolic syndrome: no adv fibrosis 36%; adv fibrosis 50% Advanced fibrosis: 95/2312 (4%) Severe steatosis: 470/2312 (20%) Both advanced fibrosis and severe steatosis: 36/2312 (1.6%) Dyslipidaemia: 1401/2312 (60.6%) Type 2 diabetes: 267/2312 (11.5%) Dyslipidaemia and type 2 diabetes:644/2312 (27.8%) Follow-up Median follow-up 12.2 years (0.1-14.5). 278/2663 were lost to follow-up. No information supplied on the differences between those lost and those included. Differences in follow-up times depending on baseline fibrosis. No advanced fibrosis (Fibrotest ≤0.48) median (range) 12.2 (0.1-14.5), median advanced fibrosis (range) 7.6 (1.3-13.6) $p<0.001$. Difference in follow-up times according to metabolic status. Dyslipidaemia 12.7 (0.1-14.5); type 2 diabetes 6.9 (0.1-9.4); dyslipidaemia + type 2 diabetes 7.4 (0.1-14.5) $p < 0.001$
Prognostic variable(s)	Advanced fibrosis determined by FibroTest >0.48 Severe steatosis (>32% hepatocytes) determined by SteatoTest >0.69
Confounders	Age, gender, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, SBP, DBP, tobacco and alcohol consumption, presence of diabetes, as well as HbA1c and for those with Type 2 diabetes also adjusted for treatment factors.

Reference	Perazzo 2014[756,756]
Outcomes and effect sizes	Diagnosis of cardiovascular-related death using the ICD-10: ischemic heart diseases (I20-I25), cardiac arrest (I46), heart failure (I50), cerebrovascular diseases (I63 and I64) and cardiogenic shock (R57.0). 172 (7.4%) died of cardiovascular disease related events during follow-up. • Adjusted HR 1.24 (0.27-5.77) for those with advanced fibrosis dying of CV-related events compared to those without advanced fibrosis • Adjusted HR 2.27 (0.75-6.89) for those with severe steatosis dying of CV-related events compared to those without severe steatosis <u>Sub-group analyses</u> Diabetes population (with or without dyslipidaemia, n=911) also adjusted for treatment (statins, fibrates, anti-diabetics and anti-platelets). • Adjusted HR 1.26 (0.06-8.31) for those with type 2 diabetes and advanced fibrosis dying of CV-related events compared to those with type 2 diabetes without advanced fibrosis • Adjusted HR 1.46 (0.21-10.27) for those with type 2 diabetes and severe steatosis dying of CV-related events compared to those with type 2 diabetes without severe steatosis
Comments	General limitations: Unclear how patients recruited (consecutive or random). Unclear attrition between prognostic risk factor groups. Unclear final mortality numbers, but there is a possibility that there could be <10 events per variable.

Reference	Pickhardt 2014[765]
Study type and analysis	Retrospective review of electronic records Multiple logistic regression analysis
Country and setting	Retrospective review of abdominal CT examinations within the radiology PACS at a single university hospital, USA
Duration of study	Initial CT March 2001 to February 2002 (initiation of routine storage in the PACS archive).
Number of participants and characteristics	n = 1050 Inclusion criteria CT scans through the liver performed without IV contrast agent in adult patients (≥18 years) for indications other than suspected liver disease. Exclusion criteria CT scans of advanced cirrhosis, hepatic malignancy (primary or secondary), or other obvious identifiable liver disease beyond steatosis. CT liver attenuation between 45-60 or >60 HU. Pre-existing liver disease at time of CT scan, alcohol abuse or alcoholism (>21 drinks/wk for men and >14

Reference	Pickhardt 2014[765]
	drinks/wk for women or a medical record diagnosis of alcoholism), < 1 year follow up. Population characteristics Mean age (SD): steatosis 51.4 (14.7); no steatosis 50.8 (17.4); *p*=0.59 Women: steatosis 53.9%; no steatosis 54.7%; *p*=0.83 Obesity (BMI ≥30 kg/m^2): steatosis 72%; no steatosis 34%; *p*<0.001 Diabetes mellitus: steatosis 35.5%; no steatosis 12.5%; *p*<0.001 Steatosis 27% Follow-up Mean clinical follow-up time (SD; range): steatosis group 7.3 (3.2; 1-11.4) years; no steatosis 7.7 (3.2; 1-11.4) years.
Prognostic variable(s)	Hepatic steatosis defined as liver attenuation of 45 HU or lower "which is well below the 100% specificity threshold for moderate or greater steatosis (defined as ≥30% fat at histopathology) particularly for GE Healthcare CT scanners". Control defined as normal liver attenuation in the range of 60-65 HU inclusive.
Confounders	Liver attenuation (as a continuous variable) or hepatic steatosis (as a categorical variable), BMI or obesity, diabetes, elevated liver enzymes. No age or gender entered in univariate or MVA. However they state narratively that "age and sex profile was similar between the two groups (see characteristics above).
Outcomes and effect sizes	Cardiovascular events including myocardial infarction (MI), cerebrovascular accident (CVA), documented transient ischemic attacks (TIAs), and coronary bypass grafting or stenting 9.9% of steatosis group and 5.9% of non steatosis group experienced post-CT cardiovascular events (*p*=0.028). When restricting just to initial cardiovascular event after the CT scan: 7.8% of steatosis group and 4.4% of non steatosis group (*p*=0.043). • Adjusted OR 1.11 (95% CI 0.553-2.228) that people with hepatic steatosis at baseline will experience a cardiovascular event compared to those without hepatic steatosis (*p*=0.77).
Comments	General limitations: Age and gender not considered at univariate or multivariate level. Unclear use of multiple raters for prognostic factor or outcome and consideration of inter-rater reliability.

Reference	Pisto 2014[771]
Study type and	Prospective cohort

Reference	Pisto 2014[771]
analysis	Cox regression analysis
Country and setting	Finland
Duration of study	Recruitment December 1990 to May 1992. Follow-up 31 December 2009 or whenever the first event occurred.
Number of participants and characteristics	n = 988 Inclusion criteria Oulu Project Elucidating Risk of Atherosclerosis (OPERA) participants (recruitment and inclusion not described in this paper). Hypertensive patients randomly selected from the national register for reimbursement of the costs of antihypertensive medication. Age-matched and sex-matched controls randomly selected from the same register. Exclusion criteria Previous hospital diagnosed myocardial infarction or stroke at baseline Population characteristics Mean age (SD): no fatty liver 50.9 (6); moderate fatty liver 51.9 (6.1); severe fatty liver 51.5 (5.5) years Males: no fatty liver 44%; moderate fatty liver 65%; severe fatty liver 60% Mean BMI (SD): no fatty liver 26.4 (3.9); moderate fatty liver 29.8 (5); severe fatty liver 31.9 (4.9) kg/m^2 Hypertension: no fatty liver 41%; moderate fatty liver 66%; severe fatty liver 72% Diabetes: no fatty liver 2%; moderate fatty liver 12%; severe fatty liver 37% Fatty liver at baseline: None 73%; Moderate 12%; Severe 15% Follow-up Median follow-up time 212 months (maximum 228)
Prognostic variable(s)	Hepatic steatosis based on liver-kidney contrast measured with ultrasonography by one trained radiologist. Normal liver parenchyma should be slightly more echogenic (brighter) than the kidney parenchyma. The severity of hepatic steatosis was based on the brightness of the liver and classified into three groups: 0=normal bright indicating a non-fatty liver, 1=medium bright, a moderate lipid content and 2=clearly bright, a sever lipid content and fatty liver. For this guideline the committee felt that US was not adequate to grade fatty liver. Therefore although this paper reports results according to moderate or severe fat content. We will only consider the severe fat content outcome.

Reference	Pisto 2014[771]
Confounders	Fat content, age, gender, LDL cholesterol, smoking, alcohol consumption, systolic blood pressure, BMI, QUICKI (quantitative insulin sensitivity check index).
Outcomes and effect sizes	Cardiovascular events based on the registry of the National Institute for Health and Welfare. CVD included a major CHD event and stroke (excluding subarachnoid haemorrhage) whichever of these happened first. CHD based on the ICD-10 (International Statistical Classification of Diseases and Related Health Problems) or if they had undergone coronary artery bypass graft surgery or angioplasty. 97/720 (13.5%) of the people with no liver fat content experienced a CVD event; 20/124 (24.2%) of the people with moderate liver fat content experienced a CVD event; 42/144 (29.2%) of the people with severe liver fat content experienced a CVD event during the follow-up time. • Severe fat content HR 1.49 (95% CI 0.97-2.30) compared to no fat content <u>Outcomes not included in review</u> • Moderate fat content HR 1.31 (95% CI 0.83-2.05) compared to no fat content
Comments	General limitations: Unclear why diabetes not included in MVA when there is a difference between groups at baseline. Does not exclude heavy drinkers (mean consumption 210g/wk in men and 140g/wk in women). However the authors report that they performed sensitivity analyses excluding the heavy drinking men and women and also excluding patients with insulin-treated diabetes mellitus, cortisone treatment at baseline and previous diagnosis for liver disease (e.g. virus medications) and that these exclusions did not have any effect on the results (raw data not provided).

Reference	Ryoo 2014[819]
Study type and analysis	Prospective study Cox proportional hazards analysis
Country and setting	Medical health check programme at the health promotion centre of a university hospital, Korea
Duration of study	Initial check-up 2005. Follow up visit between 2006-2010.
Number of participants and characteristics	n = 22090 Inclusion criteria Korean male workers. All employees participate in either annual or biennial health check-up as required by Korea's Industry Safety and Health Law. Exclusion criteria

Reference	Ryoo 2014[819]
	History of malignancy, past history of CVD, taking lipid-lowering medication, alcohol intake ≥20 g/day, elevated GGT levels, positive serologic marker for hepatitis B surface antigen or hepatitis C virus antibody, abnormal liver ultrasound findings of chronic liver disease, liver cirrhosis and/or current or past history of clonorchiasis and baseline hypertension. Population characteristics Mean age (SD): normal 42.0 (6.9); mild 42.4 (6.6); moderate to severe 40.9 (5.8) years Mean BMI (SD): normal 23.1 (2.4); mild 25.5 (2.2); moderate to severe 27.4 (2.6) kg/m^2 Mean systolic BP (SD): normal 109.9 (10.7); mild 112.0 (10.4); moderate to severe 114.9 (10.2) mmHg Mean diastolic BP (SD): normal 73.8 (7.0); mild 75.6 (6.8); moderate to severe 76.1 (6.4) mmHg Diabetes: normal 1.5%; mild 5%; moderate to severe 7.2% Fatty liver status: 65.8% normal; 30% mild; 4.5% moderate to severe. Follow-up Average (SD) follow up period of 3.62 (1.42) years. 6742/28832 excluded who did not attend follow-up visit.
Prognostic variable(s)	Diagnosis and degree of fatty liver based on the results of abdominal ultrasound with 3.5MHz transducer. Carried out by 11 radiologists (inter-observer reliability and intra-observer reliability (kappa static 0.74 and 0.94). Fatty liver diagnosed according to standard criteria (not reported) including parenchymal brightness, visualisation of portal and hepatic borders, liver-to-kidney contrast, deep beam attenuation and bright vessel walls. For this guideline the committee felt that US was not adequate to grade fatty liver. Therefore although this paper reports results according to moderate or severe fat content. We will only consider the severe fat content outcome.
Confounders	Age, BMI, triglyceride, serum creatinine, AST, ALT, GGT, recent smoking status, regular exercise, and diabetes mellitus.
Outcomes and effect sizes	Development of hypertension assessed from the annual records of all participants and defined as blood pressure ≥140/90 mmHg. Also participants who had a history of hypertension or currently using antihypertensive medication based on the self-report questionnaire at each visit were considered to have developed hypertension. 3820 (17.3%) of the total population developed incident hypertension between 2006-2010. 2092/14529 (14.4%) of men with normal liver at baseline developed hypertension; 1428/6554 (21.8%) of men with mild fatty liver at baseline developed hypertension; 303/1007 (30.1%) of men with moderate to severe fatty liver at baseline developed hypertension. • Severe fat fatty liver HR 1.14 (95% CI 1.00-1.30) for developing hypertension compared to those men with normal liver <u>Outcomes not included in review</u> • Mild fatty liver HR 1.07 (95% CI 1.00-1.15) for developing hypertension compared to those men with normal liver

Reference	Ryoo 2014[819]
Comments	General limitations: presumed consecutive sample. Unclear attrition based on baseline characteristics as original group membership not stated in loss to follow-up cohort. Unclear reporting on definition of fatty liver and confirmation of NAFLD status.

Reference	Shibata 2007 [872]
Study type and analysis	Prospective cohort Cox proportional hazards analysis
Country and setting	Single health centre, Japan
Duration of study	8 years, from 1997 to 2005
Number of participants and characteristics	N= 3189 Inclusion criteria Male workers Exclusion criteria Alcohol intake of 20 grams or greater at the time of registration and those with <1 year follow-up. Impaired glucose tolerance, impaired fasting glucose or diabetes on a 75-g oral glucose tolerance test based on criteria of the American Diabetes Association, using medications for hypertension, dyslipidaemia, liver disease, positive for markers of viral hepatitis B or C, history of coronary heart disease or stroke, gastrectomy at time of registration. Population characteristics BMI (SD): fatty liver 24.8 (2.5); no fatty liver 22.5 (2.3) kg/m^2 NAFLD at baseline: 802 (25%) No other patient characteristics present for the cohort group (only separate nested case control study not included in this review) Follow up Duration of follow up: fatty liver 3.6 (2.4) years (range 1-8 years) and non fatty liver 4.1(2.5) years (range 1-8)
Prognostic variable(s)	NAFLD was diagnosed based on the presence of fatty liver according to abdominal ultrasound by one gastroenterologist. Men with hepatorenal echo contrast and liver brightness were diagnosed as fatty liver.

Reference	Shibata 2007 [872]
Confounders	Age and BMI (male only cohort)
Outcomes and effect sizes	Diabetes was defined as fasting plasma glucose level ≥7.0 mmol/L and 2-h postload plasma glucose level ≥11.1 mmol/l on a 75-g oral glucose tolerance test. Incidence of diabetes after 8 years: 65/802 (8%) men with NAFLD; 44/2387 (1.8%) men without NAFLD • HR 5.5 (95% CI 3.6-8.5) for men with NAFLD compared to those without NAFLD.
Comments	General limitations: No detailed description of patient selection re: consecutive or random, no information of assessor blinding for NAFLD status or diabetes outcome. Unclear patient baseline characteristics considering no other variables included in MVA.

Reference	Sung 2014[934]
Study type and analysis	Retrospective cohort Logistic regression
Country and setting	Medical health check programme at the health promotion centre of a university hospital, Korea
Duration of study	Baseline examination 2003. Re-examination 2008.
Number of participants and characteristics	n = 11448 Inclusion criteria All employees required to participate in annual or biennial health examinations by the Industrial Safety and Health Law. Exclusion criteria Hypertension at baseline, missing baseline data. Population characteristics Mean age (SD): No fatty liver 40.33 (5.84); develop fatty liver 40.84 (5.58); resolve fatty liver 41.13 (5.52); maintain fatty liver 41.13 (5.52) years Male: No fatty liver 60%; develop fatty liver 84%; resolve fatty liver 86%; maintain fatty liver 91% Mean BMI (SD): No fatty liver 22.56 (2.47); develop fatty liver 24.21 (2.23); resolve fatty liver 25.39 (2.25); maintain fatty liver 25.93 (2.32) kg/m^2 Mean SBP (SD): No fatty liver 110 (10.21); develop fatty liver 113 (9.24); resolve fatty liver 113 (9.05); maintain fatty liver 114 (8.88) mmHg Mean DPB (SD): No fatty liver 70.92 (7.58); develop fatty liver 72.95 (6.85); resolve fatty liver 73.64 (6.65); maintain fatty liver 74.24 (6.4) mmHg Mean HOMA-IR (SD): No fatty liver 1.49 (0.57); develop fatty liver 1.68 (0.67); resolve fatty liver 1.93 (0.78); maintain fatty liver 2.14 (0.99)

Reference	Sung 2014[934]

	Fatty liver status:
	• No fatty liver at baseline 8489/11448 (74%)
	  ○ Maintained no fatty liver at follow-up 7071/11448 (62%)
	  ○ Developed (incident) fatty liver at follow-up 1418/11448 (12%)
	• Fatty liver at baseline 2959/11448 (26%)
	  ○ Maintained (prevalent) fatty liver at follow-up 2275/11448 (20%)
	  ○ Resolution of fatty liver at follow-up 684/11448 (6%)
	
	Follow-up
	No information provided on missing follow-up data cohort and loss to follow-up.

Prognostic variable(s)	Fatty liver diagnosed using abdominal ultrasound (3.5MHz probe) performed by experienced clinical radiologists. Fatty infiltration of the liver was identified where there was an increase in echogenicity of the liver compared with the echogenicity of the renal cortex where the diaphragm and intrahepatic vessels appeared normal.
Confounders	Age, sex, alcohol consumption, smoking status, exercise, SBP, BMI, diabetes status, GGT, HOMA-IR.
Outcomes and effect sizes	Developing incident hypertension defined if the average of two systolic and diastolic blood pressure measurements showed either a SBP ≥140 mmHg or a DBP ≥90 mmHg, and/or the person was taking antihypertensive medication. 911/11448 (8%) developed hypertension at follow-up. • Adjusted OR 1.29 (1.07-1.57) for people with fatty liver at baseline and follow-up developing hypertension compared to those without fatty liver at baseline or follow-up. • Adjusted OR 1.59 (1.30-1.95) for people with no fatty liver at baseline who developed fatty liver at follow-up also developing hypertension compared to those without fatty liver at baseline or follow-up. • Adjusted OR 1.04 (0.78-1.40) for people with fatty liver at baseline who no longer had fatty liver at follow-up developing hypertension compared to those without fatty liver at baseline or follow-up.
Comments	General limitations: Difference in baseline alcohol consumption between groups and they do not exclude heavy drinkers. Although alcohol consumption is adjusted for in the MVA the outcome effect is not reported. Presumed consecutive sample. No information about inter-rater reliability for fatty liver ultrasound diagnoses.

Reference	Targher 2007[949] with supplementary methods data from Targher 2005[947]
Study type and	Prospective cohort

Reference	Targher 2007[949] with supplementary methods data from Targher 2005[947]
analysis	Multivariate Cox proportional hazards analysis
Country and setting	Single diabetes outpatient clinic, Italy
Duration of study	January-December 2000. Follow-up through to December 2006
Number of participants and characteristics	n = 2103 Inclusion criteria All outpatients with Type 2 diabetes enrolled in the Valpolicella Heart Diabetes Study. Exclusion criteria CVD at baseline, alcohol abuse. Other known causes of chronic liver disease (viral infection or medications). Population characteristics Mean age (SD): CVD event 61 (4); no CVD event 59 (3) years Male: CVD event 63%; no CVD event 62% Mean BMI (SD): CVD event 28 (4); no CVD event 26 (3) kg/m^2 Duration of diabetes (SD): CVD event 16 (3); no CVD event 14 (3) years Metabolic syndrome: CVD event 75%; no CVD event 59% Mean SBP (SD): CVD event 131 (16); no CVD event 127 (12) mmHg Mean DBP (SD): CVD event 83 (14); no CVD event 80 (12) mmHg Hepatic steatosis at baseline: 157/2103 (7.5%) Follow-up 6.5 years of follow-up. Range 5-84 months
Prognostic variable(s)	Hepatic steatosis diagnosed by ultrasound scanning (3.5MHz transducer) by a trained observer. Hepatic steatosis was diagnosed by characteristic echo patterns, according to conventional criteria (evidence of diffuse hyperchogenicity of liver relative to kidneys, ultrasound beam attenuation, and poor visualisation of intra-hepatic structures. Repeated measurements (subgroup n = 100) on the same subjects gave intra- and inter-observer coefficients of variation within 5%.
Confounders	Age, sex, smoking, diabetes duration, HbA1c, LDL cholesterol, medications, metabolic syndrome
Outcomes and	Cardiovascular disease events composite outcome of myocardial infarction, ischemic stroke, coronary revascularisation or cardiovascular death.

Reference	Targher 2007[949] with supplementary methods data from Targher 2005[947]
effect sizes	384 total cardiovascular disease events (18%). 96/157 (61%) people with hepatic steatosis at baseline developed a CVD event. 288/1946 of people without NAFLD at baseline developed CVD event (15%). • Adjusted HR 1.87 (1.2-2.6) for people with T2D and hepatic steatosis (authors state NAFLD specifically) experiencing CVD event compared to those with T2D without hepatic steatosis (NAFLD).
Comments	General limitations: presumed consecutive sample. Population includes 10% participants who drank >20 g/day. Baseline information about whether these people were evenly distributed between hepatic steatosis group was not available, nor was alcohol consumption included in the MVA. However authors state that exclusion of participants who were light/moderate drinkers did not alter the association between hepatic steatosis and CVD risk. BMI is not included in MVA, however it is a component of metabolic syndrome and authors describe narratively that "almost identical results were obtained in models that adjusted for the individual components of metabolic syndrome (data not supplied). No attrition information provided.

Reference	Targher 2008[952]
Study type and analysis	Prospective cohort Multivariate Cox proportional hazards analysis
Country and setting	Single diabetes outpatient clinic, Italy
Duration of study	NR
Number of participants and characteristics	n = 1760 Inclusion criteria Type 2 diabetes and normal or near-normal kidney function and without overt proteinuria Exclusion criteria NR Population characteristics Mean age (SD): CKD 60 (4); no CKD 57 (3) years Male: CKD 63%; no CKD 60% Mean BMI (SD): CKD 27 (3); no CKD 26 (3) kg/m^2

Reference	Targher 2008[952]
	Duration of diabetes: CKD 14 (3); no CKD 12 (3) years Mean SBP (SD): CKD 130 (15); no CKD 127 (12) mmHg Mean DBP(SD): CKD 83 (13); no CKD 82 (11) mmHg NAFLD at baseline: 9% Follow-up 6.5 years. 67/1827 list to follow-up. No further information provided.
Prognostic variable(s)	NAFLD diagnosed by liver ultrasound and exclusion of other common causes of chronic liver disease.
Confounders	Age, gender, BMI, waist circumference, blood pressure, smoking, diabetes duration, glycosylated haemoglobin, lipid, antihypertensive, or antiplatelet drugs
Outcomes and effect sizes	Chronic kidney disease defined as over proteinuria and/or eGFR <60 ml/min per 1.73 m^2 547/1760 (31%) of total population developed CKD. 96/159 (60%) of people with NAFLD at baseline developed CKD. 451/1601 (28%) of people without NAFLD at baseline developed CKD. • Adjusted HR 1.49 (95% CI 1.1-2.2) for those with T2D and NAFLD developing CKD compared to those with T2D without NAFLD.
Comments	General limitations: no information on baseline status of those lost to follow-up. No information on how population recruited or selected. Very little information on how prognostic variable measured, including information on rater reliability.

Reference	Targher 2013[951]
Study type and analysis	Prospective cohort Cox regression analysis
Country and setting	Single diabetes clinic, Italy
Duration of study	Baseline 2000-2001. Follow-up January 2011
Number of participants and characteristics	n = 400 Inclusion criteria Random sample (using random number generator) of people with type 2 diabetes who were free from arterial fibrillation at baseline.

Reference	Targher 2013[951]
	Exclusion criteria History of AF or atrial flutter, taking anti-arrhythmic drugs, history of previous moderate-to-severe aortic and mitral valvular disease, known causes of chronic liver disease (alcohol- or drug-induced, viral hepatitis, hemochromatosis), missing liver ultrasound or laboratory data. Population characteristics Mean age (SD): NAFLD 63 (9); no NAFLD 64 (9) years Male/female: NAFLD 167/114; no NAFLD 68/51 Mean BMI (SD): NAFLD 30.7 (4.5); no NAFLD 27.1 (4.4) kg/m^2 Median diabetes duration (IQR): NAFLD 5 (1-13); no NAFLD 7 (1-10) years Mean SBP (SD): NAFLD 141 (15); no NAFLD 138 (14) mmHg Mean DBP (SD): NAFLD 81 (7); no NAFLD 80 (7) mmHg Hypertension: NAFLD 73%; no NAFLD 65% NAFLD at baseline: 281 (70.2%) Follow-up The ascertainment at the end of the follow-up period for the whole sample was 100%
Prognostic variable(s)	Hepatic steatosis diagnosed using ultrasonography performed by a single radiologist. Defined on the basis of characteristic sonographic features: evidence of diffuse hyper-echogenicity of the liver relative to the kidneys, ultrasound beam attenuation and poor visualisation of intra-hepatic vessel borders and diaphragm. NAFLD diagnosis hepatic steatosis on ultrasound among persons who drank < 20g/day of alcohol and who did not have viral hepatitis, drug-induced liver disease, iron overload, or other secondary causes of liver disease.
Confounders	Age, sex, hypertension electrocardiographic LVH and PR interval, 10-year Framingham Heart Study-derived AF risk score (age, sex BMI, SPB, hypertension treatment, ECG PR interval and history of heart failure).
Outcomes and effect sizes	Atrial fibrillation or atrial flutter present on standard ECG obtained from either routine clinic examination or from reviewing hospital and physician charts. Diagnosis was confirmed by a cardiologist blinded to NAFLD status. During the 10 year follow up 42 people developed incident arterial fibrillation (10.5%). 38/281 (13.5%) people with T2D and NAFLD developed AF. 4/119 (3.4%) of people with T2D without NAFLD developed AF. • Adjusted OR 4.96 (95% CI 1.4-17.0) for people with T2D and NAFLD developing AF compared to those with T2D without NAFLD. <u>Sensitivity analyses excluding those with documented history of CHD and heart failure (n = 47)</u> • Adjusted OR 3.78 (95% CI 1.1-13.2) for people with T2D and NAFLD developing AF compared to those with T2D without NAFLD.

Reference	Targher 2013[951]
Comments	General limitations: Less than 10 outcome events per variable make the analysis unstable and suggest a concern with the results.

Reference	Targher 2014[950]
Study type and analysis	Retrospective database cohort Multivariate Cox proportional hazards analysis
Country and setting	Diabetes outpatient clinic, Italy
Duration of study	Baseline 1999-2001. Follow up 31 May 2013
Number of participants and characteristics	n = 261 Inclusion criteria All Caucasian type 1 diabetes outpatients with preserved kidney function (eGFR ≥60 mL/min/1.73 m^2) and with no macroalubuminuria who regularly attended adult diabetes clinic Exclusion criteria No available liver ultrasound, documented history of cancer, cirrhosis, myocardial infarction, angina, and coronary revascularisation procedures, secondary causes of chronic liver disease such as excessive alcohol consumption (>30g/day men and >20g/day women), viral hepatits and drug-induced liver disease. Population characteristics Mean age (SD): NAFLD 45 (12); no NAFLD 38 (12) years Male/female: NAFLD 68/63; no NAFLD 48/82 Mean BMI (SD): NAFLD 26.3 (4.9); no NAFLD 22.7 (3.41) kg/m^2 Median diabetes duration (IQR): NAFLD 21 (14-33); no NAFLD 14 (9-20) years Mean SBP (SD): NAFLD 133 (17); no NAFLD 124 (16) mmHg (p <0.001) – not adjusted for in MVA. Mean DBP (SD): NAFLD 80 (9); no NAFLD 76 (8) mmHg (p <0.005) – not adjusted for in MVA. Hypertension: NAFLD 60%; no NAFLD 27% Metabolic syndrome: NAFLD 52%; no NAFLD 18% (p <0.001) – not adjusted for in MVA. NAFLD at baseline: 50.2%

Reference	Targher 2014[950]
	Follow-up No participants were lost to follow-up
Prognostic variable(s)	Hepatic steatosis based on ultrasonography by two experienced radiologists. Hepatic steatosis diagnosed on the basis of characteristic ultrasonographic features – evidence of diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualisation of the intrahepatic vessel borders and diaphragm. Intra-and inter-observer variabilities were within 5%.
Confounders	Age, sex, duration of diabetes, HbA1c, hypertension, baseline eGFR, BMI and serum triglycerides.
Outcomes and effect sizes	Development of incident CKD defined as the occurrence of eGFR <60 mL/min/1.73 m2 and/or macroalbuminuria. Both of these outcomes were confirmed in all participants in at least 2 consecutive occasions. 61/261 developed CKD. 46/131 (35%) people with NAFLD developed CKD. 15/130 (11/5%) of people without NAFLD developed CKD. • Adjusted HR 2.02 (95% CI 1.08-3.83) for those with type 1 diabetes and NAFLD developing CKD compared to those with type 1 diabetes without NAFLD. <u>Sensitivity analysis excluding those with microalbuminuria at baseline (n = 27)</u> • Adjusted HR 1.85 (95% CI 1.03-3.27) for those with type 1 diabetes and NAFLD developing CKD compared to those with type 1 diabetes without NAFLD.
Comments	General limitations: Presumed consecutive sample. No attrition. Initially BMI not included in MVA due to insignificance at univariate level, however there was a significant difference at baseline. However authors added BMI in a later sensitivity analysis and so those results are provided here (very little difference from original result of HR 2.03 (1.10-3.77)). There are baseline difference between NAFLD groups for blood pressure and metabolic syndrome, however these are not adjusted for in the MVA.

Reference	Wong 2011[1041]
Study type and analysis	Prospective cohort study Multivariable logistic regression
Country and setting	Single centre hospital, Hong Kong
Duration of study	Follow-up analysis once the last recruited patient reached 1 year follow-up.
Number of participants	n = 612

Reference	Wong 2011[1041]
and characteristics	Inclusion criteria Consecutive adult patients aged ≥18 years who underwent coronary angiogram (clinical indications for coronary angiogram). Exclusion criteria Contraindications to coronary angiogram, excessive alcohol intake (>20 g/day in men and 10 g/day in women) and secondary causes of fatty liver (chronic use of systemic corticosteroids or methotrexate). Positive hepatitis B surface antigen, antibody against hepatitis C virus and antinuclear titre >1/160. Patients undergoing emergency primary percutaneous coronary intervention for acute myocardial infarction. Population characteristics Mean age (SD): Fatty liver 63 (10); no fatty liver 63 (12) years Male: Fatty liver 74%; no fatty liver 63% Mean BMI (SD): Fatty liver 25.7 (4); no fatty liver 23.2 (3.1) kg/m^2 Diabetes: Fatty liver 41%l no fatty liver 17% Hypertension: Fatty liver 71%; no fatty liver 58% Mean SBP (SD): Fatty liver 140 (22); no fatty liver 132 (21) mmHg Mean DBP (SD): Fatty liver 77 (13); no fatty liver 72 (13) mmHg Fatty liver status: 356/612 (58%) of people had fatty liver at baseline. Follow-up Mean follow-up time (SD): Fatty liver 89 (19); no fatty liver 85 (25) weeks. No attrition information reported.
Prognostic variable(s)	Fatty liver based on ultrasonographic features of diffusely increased liver echogenicity greater than that of the kidney or spleen, vascular blurring and deep attenuation of the ultrasound signal. Performed by two investigators.
Confounders	Fatty liver, age, gender, diabetes, waist circumference, fasting glucose, HDL-cholesterol, ALT. BMI, SBP and DBP were not significant at univariate level so were not included in MVA.
Outcomes and effect sizes	Coronary artery disease based on cardiac catheterisation findings reviewed by at least two experienced cardiologists. Significant CAD defined as the presence of at least 50% stenosis at one or more major coronary arteries. 301/356 (84.5%) of people with fatty liver developed significant coronary artery disease. 164/256 (64%) of people without fatty liver developed CAD. • Adjusted OR 2.13 (95% CI 1.46-3.64) for people having coronary angiogram with NAFLD developing CAD compared to those people having coronary angiogram without NAFLD.

Reference	Wong 2011[1041]
Comments	General limitations: Population slightly indirect due to clinical indication for coronary angiogram (specifically). Short follow up time (just over a year and a half). No attrition information supplied. No inter- or intra-rater variability calculations supplied.

Reference	Yamada 2010[1055]
Study type and analysis	Retrospective cohort Multivariable logistic regression
Country and setting	Japan
Duration of study	Baseline assessment in 2000. Follow-up 2005
Number of participants and characteristics	n = 12375 Inclusion criteria Participants undergoing medical health check-ups including ultrasound. Exclusion criteria Past and present diabetes mellitus, hepatic diseases, positive results for hepatitis viruses, fasting hyperglycemia. Population characteristics Male/female: 6799/5576 Mean age (SD): Male fatty liver 48.1 (0.6); male no fatty liver 49.5 (10.7); female fatty liver 53.7 (8.8); female no fatty liver 50.3 (9.3) years Mean BMI (SD): Male fatty liver 25.3 (2.7); male no fatty liver 22.4 (2.5); female fatty liver 25.2 (3.0); female no fatty liver 21.8 (2.6) kg/m2 Mean SBP (SD): Male fatty liver 122.8 (16.3); male no fatty liver 117.0 (16.6); female fatty liver 124.5 (17.2); female no fatty liver 114.4 (16.7) mmHg Mean DBP (SD): Male fatty liver 77.1 (10.6); male no fatty liver 73.4 (10.9); female fatty liver 76.2 (11.1); female no fatty liver 70.5 (10.6)) mmHg Family history of diabetes: Male fatty liver 14.7%; male no fatty liver 12%; female fatty liver 19.8%; female no fatty liver 14.8% Daily drinker: Male fatty liver 35.5%; male no fatty liver 48.5%; female fatty liver 4.9%; female no fatty liver 8.5% Fatty liver: 5303/6799 (78%) of males; 3976/5576 (71.3%) of females. Follow-up

Reference	Yamada 2010[1055]
	No attrition data provided. No mean outcome data provided.
Prognostic variable(s)	Abdominal ultrasonographic examination was performed by 10 technicians. Fatty liver assessed according to the modified criteria of liver brightness (diagnosed by difference of more than 10 from the average of liver and renal cortical echo amplitudes), attenuation of echo penetration and decreased visualisation of veins were included as criteria.
Confounders	Age, BMI, alcohol drinking, smoking, family history of diabetes, fatty liver. Gender not included in MVA but results reported separately.
Outcomes and effect sizes	Incidences of newly diagnosed impaired fasting glucose (IFG) or type 2 diabetes (T2D). IFG defined as fasting blood glucose values between 110 and 125 mg/dL. T2D was defined as fasting blood glucose value of ≥126 mg/dL 154/5303 (2.9%) of men with fatty liver developed T2D compared to 9/1496 (0.6%) of men without fatty liver. 562/5303 (10.6%) of men with fatty liver developed IFG compared to 78/1496 (5.2%) of men without fatty liver. 79/3976 (2.0%) of women with fatty liver developed T2D compared to 7/1600 (0.4%) of women without fatty liver. 374/3976 (9.4%) of women with fatty liver developed T2D compared to 42/1600 (2.6%) of women without fatty liver. • Adjusted OR 1.91 (95% CI 1.56-2.34) for men with NAFLD developing IFG or T2D compared to men without NAFLD • Adjusted OR 2.15 (95% CI 1.53-3.01) for women with NAFLD developing IFG or T2D compared to women without NAFLD
Comments	General limitations: unclear how patients recruited – consecutive or random? Daily drinkers not excluded but drinking included in MVA. No attrition data provided. Combined outcome in MVA of IFG and T2D – indirect outcome compared to review protocol. No information on inter- or intra-observer variability.

Reference	Yamazaki 2015 [1056]
Study type and analysis	Retrospective cohort Logistic regression analysis
Country and setting	Single medical healthcare centre, Japan
Duration of study	2000 to 2012
Number of participants and characteristics	n = 3074 Inclusion criteria Japanese participants who received an abdominal ultrasound health check between 200 and 2012 with an interval of >10 years between the health checks.

Reference	Yamazaki 2015 [1056]
	Exclusion criteria Positive serologic marker for hepatitis B surface antigen or hepatitis C antibody, alcohol intake > 20 g/day or diabetes at baseline. Population characteristics: By baseline NAFLD status Mean age (SD): NAFLD 43.8 (7.3); no NAFLD 43 (7.2) years Mean BMI (SD): NAFLD 26.0 (2.9); no NAFLD 21.8 (2.5) kg/m^2 Hypertension: NAFLD 19.9 %; no NAFLD 8.4% Dyslipidaemia: NAFLD 65.9%; no NAFLD 26.4% NAFLD at baseline: 24% (728/3074) Follow up Mean (SD) interval between health checks: 11.3 (0.8) years NAFLD improvement (110/728) NAFLD sustained (618/728)
Prognostic variable	NAFLD after exclusion of hepatitis B, hepatitis C and ethanol intake > 20 g/day. Fatty liver diagnosed on ultrasound. Ascertained by the discrepancy of echo amplitude between liver and the kidney with increased liver echogenicity. 'Improved NAFLD' diagnosed by having NAFLD at baseline but not at the second visit. Abdominal US performed by those who had no knowledge of study objective and inspected by physicians who had no knowledge of study.
Confounders	Age, sex, BMI, impaired fasting glucose, family history of diabetes, dyslipidaemia, hypertension, physical exercise.
Outcomes and effect sizes	Type 2 diabetes incidence defined by fasting plasma glucose ≥126 ,g/dL, HbA1c ≥6.5%, self-reported physician-diagnosed diabetes, or taking medication for diabetes. 189/3074 (6.1%) developed diabetes. 117/728 (16.1%) of people with NAFLD at baseline developed T2D at follow-up 72/2346 (3.1%) of people without NAFLD at baseline developed T2D at follow-up NAFLD vs. no NAFLD by gender 100/611 (16.4%) of men with NAFLD at baseline developed T2D at follow-up 48/1255 (3.8%) of men without NAFLD at baseline developed T2D at follow-up

Reference	Yamazaki 2015 [1056]
	17/117 (14.5%) of women with NAFLD at baseline developed T2D at follow-up 24/1091 (2.2%) of women without NAFLD at baseline developed T2D at follow-up • Adjusted OR 2.27 (95% CI 1.74-3.51) for men with fatty liver developing diabetes compared to men without fatty liver • Adjusted OR 3.01 (95% CI 1.18-7.68) for women with fatty liver developing diabetes compared to women without fatty liver Improved vs. sustained NAFLD 7/110 (6.4%) people with improved NAFLD developed T2D 110/618 (17.8%) people with sustained NAFLD developed T2D • Adjusted OR 0.27 (95% CI 0.12-0.61) for people with improved NAFLD developing diabetes compared to those with sustained NAFLD
Comments	General limitations: Unclear how patients recruited. No attrition data reported due to retrospective nature of study design. Unclear if inter-rater reliability.

H.6 Dietary modifications and supplements

Study	Alisi 2014[38]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Italy; Setting: Italian children's hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Combination of physical findings at examination, elevated amiontransferase (ALT) levels (up to 40UI/l) of unknown origin and ultrasonographic evidence of hepatic steatosis as well as histological evaluation of liver biopsies obtained at entry by an expert pathologist.
Stratum	Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined)
Subgroup analysis within study	Not applicable
Inclusion criteria	Obese children with NAFLD. Obesity diagnosed as BMI >85th percentile.

Exclusion criteria	The presence of liver disease due to any of the following: hypothyroidism, Wilson disease, viral hepatitis (HBV, HCV), acute systemic disease, cystic fibrosis, coeliac disease, suspicion of muscular dystrophy, alpha-1-antitrypsin deficiency, metabolic inherited diseases, autoimmune hepatitis, drug toxicity and drugs known to induce steatosis (e.g. valproate, amiodarone or prednisone). People were also excluded if body weight and carbohydrate metabolism were altered by the use of parenteral nutrition, protein malnutrition, previous gastrointestinal surgery, structural abnormalities of the gastrointestinal tract or neurological impairment. The use of NSAIDS, antibiotics, probiotics or anti-secretory drugs capable of causing achlorhydira within 2 months preceding enrolment were also exclusion criteria.
Age, gender and ethnicity	Age - Median (IQR): Median (IQR); placebo 11 (10,12), VSL 10 (9,12) years. Gender (M:F): 24/20. Ethnicity: Not reported
Further population details	
Extra comments	Please see baseline characteristics in extra comments.. Unclear what top age range for children was, assumed to be under 18.Probiotics vs control mean (SD); ALT (U/l) 34 (1) versus 42 (1), BMI (kg/m2) 27.1 (0.01) vs 25.6 (0.01). Probiotics vs control median (IQ); weight (kg) 65.0 (55.7,70.5) vs 53.9 (47.8, 65.0), AST (U/l) 56 (51,70) vs 63 (53,74), HOMA 3.9 (2.7,5.4) vs 3.1 (2.3,4.7). Probiotics vs control non-alcoholic steatohepatitis score (NAS) stage 3 n (%); 4.5 (2 9) vs 3 (1). Probiotics vs control NAS stage 4 n (%); 4 (18.23) versus 3 (13.6). Probiotics vs control NAS stage 5 n (%); 3 (13.6) vs 5 (22.7). Probiotics vs control NAS stage 6 n (%); 6 (27.3) vs 9 (40.9). Probiotics vs control NAS stage 7 n (%); 5 (22.7) vs 4 (18.2).Probiotics vs control NAS stage 8 n (%); 2 (9.1) vs 0 (0.0).
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Dietary supplements - Probiotics. VSL#3 1 sachet/day is aged <10 years, 2 sachets if aged ≥10 years.. Duration 4 months. Concurrent medication/care: Concurrent medication/care: A low calorie diet was also prescribed: carbohydrate 50-60%, fat 23-30%, fatty acid two-thirds saturated, one-third unsaturated protein 15-20%, for a total of 25-30 Kcal/kg bodyweight/day. A moderate programme of aerobic exercise (3--45 min at least 3 times a week) was also recommended and tailored to individual preferences (n=36) Intervention 2: Placebo / active control - Placebo. Blinded placebo sachets (1 sachet/day if aged <10 years, 2 sachets/day if aged ≥10 years). Duration 4 months. Concurrent medication/care: A low calorie diet was also prescribed: carbohydrate 50-60%, fat 23-30%, fatty acid two-thirds saturated, one-third unsaturated protein 15-20%, for a total of 25-30 Kcal/kg bodyweight/day. A moderate programme of aerobic exercise (3--45 min at least 3 times a week) was also recommended and tailored to individual preferences
Funding	Study funded by industry (Equipment / drugs provided by industry (Study funded by the Italian Ministry of Health, VSL#3 and placebo provided by VSL pharmaceuticals Inc.))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROBIOTICS versus PLACEBO

Protocol outcome 1: NAFLD progression with liver biopsy at ≥3 months to <12 months - Actual outcome for Young people (11 years or older and younger than 18 years): ALT (U/l) at 4 months; Group 1: mean 33 (SD 5.48); n=30, Group 2: mean 50 (SD 29.1); n=34; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people (11 years or older and younger than 18 years): BMI at 4 months; Group 1: mean 24.9 (SD 1.58); n=30, Group 2: mean 25.7 (SD 1.68); n=34; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	**Aller 2011[46]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)

Countries and setting	Conducted in Spain; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Percutaneous liver biopsy
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	NAFLD confirmed with percutaneous liver biopsy.
Exclusion criteria	Hepatitis B, C, cytomegalovirus, Epstein Barr infections, non organ-specific autoantibodies, alcohol consumption, diabetes mellitus, impaired glucose tolerance, blood-pressure-lowering medication or statins, hereditary defects (iron and copper storage diseases and alpha-antitrypsin deficiency).
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Group 1 (probiotic): 49.4 (10.9), group 2 (placebo): 44.3 (15.1) years. Gender (M:F): 20:8. Ethnicity: Not stated
Further population details	
Extra comments	. Probiotic versus control group, mean (SD); weight (kg) 83.5 (15.9) versus 88.8 (14.1), BMI (kg/m2) 30.2 (4.5) versus 29.5 (5.5), ALT (U/l) 67.7 (2.5) versus 60.7 (32.1), AST (U/l) 41.3 (15.5) versus 37.1 (8.2), ultrasound Doppler perfusion index 0.13 (0.05) versus 0.13 (0.05).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Dietary supplements - Streptococcus thermophilus and Lactobacillus delbrueckii subsp. bulgaricus (Lactobacillus bulgaricus). 1 tablet per day 500 million Lactobacillus bulgaricus and Streptococcus thermophilus. Duration 3 months. Concurrent medication/care: Not stated (n=15) Intervention 2: Placebo / active control - Placebo. Placebo: 120 mg starch. Duration 3 months. Concurrent medication/care: Not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STREPTOCOCCUS THERMOPHILUS AND LACTOBACILLUS DELBRUECKII SUBSP. BULGARICUS (LACTOBACILLUS BULGARICUS) versus PLACEBO

Protocol outcome 1: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): ALT at 3 months; Group 1: mean 60.4 U/l (SD 30.4); n=14, Group 2: mean 64.8 U/l (SD 35.5); n=14; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults (18 years and over): AST at 3 months; Group 1: mean 35.6 U/l (SD 10.4); n=14, Group 2: mean 36.4 U/l (SD 13.8); n=14; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	**Argo 2015**[76]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=34)
Countries and setting	Conducted in USA; Setting: Hepatology clinic

Line of therapy	Unclear
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Biopsy
Stratum	Adults (18 years and over):
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis from biopsy with steatohepatitis, defined as steatosis with inflammation, hepatocellular ballooning and/or fibrosis were included. Ethanol consumption <30g/day for males or 20g/day for females.
Exclusion criteria	People with viral hepatitis, autoimmune and metabolic liver diseases. Subjects diagnosed with cirrhosis or secondary forms of steatohepatitis or subjects treated with thiazolidinediones were also excluded.
Recruitment/selection of patients	Patients with a liver biopsy within six months of projected enrolment were eligible for consideration.
Age, gender and ethnicity	Age - Mean (SD): 46.8 (11.9). Gender (M:F): 38.2% M, 61.8% F. Ethnicity: 97% caucasian
Further population details	
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Dietary supplements - Omega fatty acids. n-3 PUFA 3000mg/day (each 100mg capsule contained 70% total n-3s in form of triglycerides: 35% eicosapentaenoic acid (EPA), 25% docosahexanoic acid (DHA), 10% other n-3s and a scant amount of lemon oil).. Duration 1 year. Concurrent medication/care: Counselling at each visit to maintain an aerobic exercise goal of 150 min/week and a hypocaloric diet with 500-1000 calories less than the estimated age- and weight-based basal metabolic rate and a fat content less than 30% of the total calories. Cardiopulmonary fitness testing consisted of a graded ergometer exercise protocol with increasing power output to measure peak volume of oxygen consumption. A nutritionist performed dietary counselling. (n=20) Intervention 2: Placebo / active control - Placebo. Identical appearing capsules, containing predominantly soybean oil but also small amounts of fish and lemon oils (only 8% n-3) to protect blinding.. Duration 1 year. Concurrent medication/care: Counselling at each visit to maintain an aerobic exercise goal of 150 min/week and a hypocaloric diet with 500-1000 calories less than the estimated age- and weight-based basal metabolic rate and a fat content less than 30% of the total calories. Cardiopulmonary fitness testing consisted of a graded ergometer exercise protocol with increasing power output to measure peak volume of oxygen consumption. A nutritionist performed dietary counselling.
Funding	Equipment / drugs provided by industry (Study supported by an NIH NCCAM grant, medication and placebo provided by Nordic Natural.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA FATTY ACIDS versus PLACEBO

Protocol outcome 1: NAFLD progression with liver biopsy at ≥12 months
- Actual outcome for Adults (18 years and over): NAS at 12 months; OR 1.53 (95%CI 0.27 to 9.72); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: NAFLD progression with MRI / MRS at ≥12 months
- Actual outcome for Adults (18 years and over): MRI Dixon fat (%) at 12 months; Group 1: mean 8.4 (SD 5.2); n=17, Group 2: mean 12 (SD 5.6); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults (18 years and over): Image fat (%) at 12 months; Group 1: mean 16.4 (SD 11.4); n=17, Group 2: mean 14.3 (SD 5.8); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months
- Actual outcome for Adults (18 years and over): ALT (U/L) at 12 months; Group 1: mean 56.7 (SD 28.3); n=17, Group 2: mean 52.8 (SD 31); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight loss at ≥12 months
- Actual outcome for Adults (18 years and over): Weight (kg) at 12 months; Group 1: mean 93.7 (SD 22.9); n=17, Group 2: mean 88.8 (SD 16.2); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver

	biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	**Eslamparast 2014[282]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Iran; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 28 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Steatosis on ultrasound associated with persistently raised ALT >50 U/l for 6 months
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Steatosis on ultrasound associated with persistently raised ALT >50 U/l for 6 months.
Exclusion criteria	Viral hepatitis, alcohol use, other causes of chronic liver disease, diabetes mellitus, untreated hypothyroidism, clinically or biochemically recognised systemic diseases, psychiatric disorders impairing the patient's ability to provide written informed consent, pregnancy, lactation, lack of effective birth control in women of childbearing age; <18 years.
Recruitment/selection of patients	Recruited from Haraz clinic in Amol, Iran
Age, gender and ethnicity	Age - Mean (SD): 46.0 (9.2) years. Gender (M:F): 25:27. Ethnicity: Not stated
Further population details	
Extra comments	. Probiotic versus control group, mean (SD); weight (kg) 85.7 (10.0) versus 81.5 (13.2), BMI (kg/m2) 32.1 (2.4) versus 31.3 (2.3), ALT (U/l) 69.3 (2.5) versus 71.5 (9.1), AST (U/l) 66.4 (2.6) versus 68.3 (9.4), transient elastography (kPa) 9.4 (1.9) versus 7.9 (2.1).
Indirectness of population	No indirectness

Interventions	(n=26) Intervention 1: Dietary supplements - Streptococcus thermophilus and Lactobacillus delbrueckii subsp. bulgaricus (Lactobacillus bulgaricus). Synbiotic capsule: 200 million of 7 strains of friendly bacteria (Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus) and prebiotic (fructooligosaccharide) and probiotic cultures (magnesium stearate [mineral and vegetable source]) and a vegetable capsule (hydroxypropyl methyl cellulose); twice daily. Duration 28 weeks. Concurrent medication/care: Advised to follow an energy-balanced diet and physical activity recommendations according to the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults from the NIH and the North American Association for the Study of Obesity (n=26) Intervention 2: Placebo / active control - Placebo. Placebo (maltodextrin). Duration 28 weeks. Concurrent medication/care: Advised to follow an energy-balanced diet and physical activity recommendations according to the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults from the NIH and the North American Association for the Study of Obesity
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STREPTOCOCCUS THERMOPHILUS AND LACTOBACILLUS DELBRUECKII SUBSP. BULGARICUS (LACTOBACILLUS BULGARICUS) versus PLACEBO

Protocol outcome 1: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): ALT at Week 28; Group 1: mean -25.1 IU/L (SD 2.86); n=26, Group 2: mean -7.3 IU/L (SD 5.72); n=26; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults (18 years and over): AST at Week 28; Group 1: mean -31.3 IU/L (SD 2.08); n=26, Group 2: mean -7.9 IU/L (SD 8.19); n=26; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: NAFLD progression with fibroscan/ transient elastography at >3 months to <6months
- Actual outcome for Adults (18 years and over): Transient elastography at Week 28; Group 1: mean -2.98 U/L (SD 1.54); n=26, Group 2: mean -0.77 U/L (SD 1.36); n=26; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse event at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Serious adverse event at Week 28; Group 1: 0/26, Group 2: 0/26; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; NAFLD

	progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	**Janczyk 2015**[463]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=76)
Countries and setting	Conducted in Poland; Setting: 4 Polish pediatric departments.
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Raised ALT and liver ultrasound or liver histology consistent with NAFLD/NASH
Stratum	Young people (11 years or older and younger than 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	All of the following: Age over 5 and below 19 years; overwieght or obesity (BMI>90pc according to IOTF BMI charts); ALT activity at least 1.3 upper limit of normal; hyperechogenicity of the liver on ultrasound or liver histology consistent with

	NAFLD/NASH (at least 5% of hepatocytes with macroesicular fat).
Exclusion criteria	Any pathologic condition affecting liver as HBV, HCV infection, chronic and acute liver failure, chlestasis, metabolic disease like alpha1-antitiprsin deficiency, Wilson disease, diabetes mellitus, hypothyroidism etc. Current or history of significant alcohol consumption, or unlikely to co-operate in the study, to comply with study treatment or with the study visits. Treatment with viatmin E, statins, UDCA, probiotics or metformin within 3 months prior to randomization. Pharmacological treatment of hypertension within 3 months prior to randomization. History of parenteral nutrition.
Recruitment/selection of patients	Eligile patients were randomised into blocks of 4individuals, stratified by centre. Randomization was genrated centrally by computer and sent by fax to the centres.
Age, gender and ethnicity	Age - Median (IQR): 13 (11.2-15.2). Gender (M:F): 11% female. Ethnicity: Not stated
Further population details	
Extra comments	Baseline values: BMI pacebo 28.86, Omega3 28.6; BMI z score Placebo 2.7, Omega3 3.0; Weight kg Placebo 73, Omega3 77.7;ALT U/L placebo 80, Omega3 79; AST U/L Placebo 48, Omega3 42.
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Dietary supplements - Omega fatty acids. Omega-3 LC-PUFA (DHA and eicosapentaenoic acid [EPA] in a 3:2 proportion [450-1300mg/day]). Administered orally twice a day. Dose dependent on patient weight.. Duration 24 weeks. Concurrent medication/care: Regular instruction by an experienced dietician to comply with an individually prescribed diet, which, in combination with increased physical activity, was aimed at producing a slow reduction in body weight (approximately 0.5kg/week). (n=39) Intervention 2: Placebo / active control - Placebo. Identical brown oval shaped capsules. Administered orally twice a day.. Duration 24 weeks. Concurrent medication/care: Regular instruction by an experienced dietician to comply with an individually prescribed diet, which, in combination with increased physical activity, was aimed at producing a slow reduction in body weight (approximately 0.5kg/week).
Funding	Academic or government funding (Polish Ministry of Science and Higher Education)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA FATTY ACIDS versus PLACEBO

Protocol outcome 1: Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months
- Actual outcome for Young people (11 years or older and younger than 18 years): ALT U/L at 6 months; Other: 0.13 (p value); Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people (11 years or older and younger than 18 years): AST U/L at 6 months; Other: 0.04 (P value); Risk of bias: Low; Indirectness of outcome:

No indirectness Protocol outcome 2: Weight loss at ≥3 months to <12 months - Actual outcome for Young people (11 years or older and younger than 18 years): Weight reduction at least 5% at 6 months; Group 1: 5/30, Group 2: 7/34; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people (11 years or older and younger than 18 years): BMI reduction at least 5% at 6 months; Group 1: 12/30, Group 2: 5/34; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Any adverse event at 3 months or greater - Actual outcome for Young people (11 years or older and younger than 18 years): Mild abdominal discomfort at 6 months; Group 1: 1/30, Group 2: 1/34; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Weight (kg) at ≥3 months to <12 months - Actual outcome for Young people (11 years or older and younger than 18 years): BMI z score at 6 months; Other: 0.83 (P value); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Severe adverse events at 3 months or greater; Serious adverse

	event at 3 months or greater; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	**Nobili 2013[698]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Italy; Setting: Outpatients at a Liver Research Unit.
Line of therapy	Unclear
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Persistently elevated serum alanine transaminase, diffusely hyperechogenic liver at ultrasonography and liver biopsy consistent with NAFLD.
Stratum	Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined)
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Consecutive children attending the unit.
Age, gender and ethnicity	Age - Median (IQR): 11 (3). Gender (M:F): Define. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Dietary supplements - Omega fatty acids. Docosahexaenoic acid (DHA) 250mg/day. Duration 1 year. Concurrent medication/care: Balanced low-calorie diet was prescribed and physical activity was suggested to all patients as described in detail elsewhere. Reinforcement of lifestyle changes were made at all visits. (n=20) Intervention 2: Dietary supplements - Omega fatty acids. DHA 500mg/day. Duration 1 year. Concurrent medication/care: Balanced low-calorie diet was prescribed and physical activity was suggested to all patients as described in detail elsewhere. Reinforcement of lifestyle changes were made at all visits. (n=20) Intervention 3: Placebo / active control - Placebo. Identical placebo pills. Duration 1 year. Concurrent

	medication/care: Balanced low-calorie diet was prescribed and physical activity was suggested to all patients as described in detail elsewhere. Reinforcement of lifestyle changes were made at all visits.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA FATTY ACIDS versus PLACEBO Protocol outcome 1: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months - Actual outcome for Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined): Change in ALT - only reported in graphical format at 6, 12, 18 and 24 months; Other: ; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 2: Weight loss at ≥12 months - Actual outcome for Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined): BMI at 6, 12, 18 and 24 months; Other: ; Risk of bias: ; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3

	months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	**Pacifico 2015[731]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=58)
Countries and setting	Conducted in Italy; Setting: Hepatology outpatient clinic
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: MRI diagnosed NAFLD [hepatic fat fraction ≥ 5%] and liver biopsy consistent with NAFLD
Stratum	Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined)
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged < 18 years, BMI > 85th percentiles according to age and gender-specific percentiles, persistently elevated aminotransferase levels, MRI diagnosed NAFLD [hepatic fat fraction ≥ 5%] and liver biopsy consistent with NAFLD
Exclusion criteria	Secondary causes of steatosis including hepatic virus infections, autoimmune hepatitis, metabolic liver disease, alpha-1 antitrypsin deficiency, cystic fibrosis, Wilson's disease, hemochromatosis, and celiac disease. Smoking, history of type 1 or 2 diabetes, renal disease, total parenteral nutrition, alcohol intake, use of hepatoxic medications and previous use of n-3 LC-PUFAs
Recruitment/selection of patients	Suspected of NAFLD between May 2012 - September 2014
Age, gender and ethnicity	Age - Mean (SD): DHA 11 (2.6) years; Placebo 10.8 (2.8) years. Gender (M:F): 30/21. Ethnicity: Not reported
Further population details	
Extra comments	Baseline details - BMI: DHA 28.9 (4.3), placebo 27.5 (5.5); ALT: DHA 57 (20), placebo 56 (19); HDL-C: DHA 41 (10), placebo 47 (9); NAS score: DHA 4.4 (0.6), placebo 4.6 (0.5); % with NASH: DHA 64%, placebo 65.4%
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: Dietary supplements – Omega fatty acids. Docosahexaenoic acid (DHA) supplementation: 250mg/day (30% DHA algae oil). Duration 6 months. Concurrent medication/care: A balanced low-calorie diet was prescribed to all patients with a recommendation to engage in a moderate daily exercise program (60 min/day at least 5

	days a week), and to reduce sedentary activities. Specifically, diet was hypocaloric (25-30 calories/kg/day), consisting of carbohydrate (50-60%), protein (15-20%), and fat (23-30%) with a composition of two in third unsaturated and one in third saturated. (n=29) Intervention 2: Placebo / active control - Placebo. Placebo (290 mg linoleic acid supplied with germ oil). Duration 6 months. Concurrent medication/care: A balanced low-calorie diet was prescribed to all patients with a recommendation to engage in a moderate daily exercise program (60 min/day at least 5 days a week), and to reduce sedentary activities. Specifically, diet was hypocaloric (25-30 calories/kg/day), consisting of carbohydrate (50-60%), protein (15-20%), and fat (23-30%) with a composition of two in third unsaturated and one in third saturated.
Funding	Academic or government funding (Sapienza University of Rome)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA FATTY ACIDS (DHA) versus PLACEBO Protocol outcome 1: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months - Actual outcome for Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined): ALT at 6 months; Group 1: mean 27 I/U (SD 14); n=25, Group 2: mean 45 I/U (SD 22); n=26; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Weight loss at ≥3 months to <12 months - Actual outcome for Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined): BMI (kg/m2) at 6 months; Group 1: mean 27.3 mg/m2 (SD 4.1); n=25, Group 2: mean 27.2 mg/m2 (SD 5.4); n=26; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: NAFLD progression with MRI / MRS at >3 months to < 6 months - Actual outcome for Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined): MRI measured hepatic fat fraction at 6 months; Group 1: mean 53.4 % decrease (SD 48.452); n=25, Group 2: mean 22.6 % decrease (SD 40.6032); n=26; Percentage 1-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with

	liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	**Sanyal 2014**[832]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=243)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Liver biopsy confirmed NASH
Stratum	Adults (18 years and over)
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Adults with borderline or definite steatohepatitis and a NAFLD activity score of at least 4 with a minimum score of 1 each for steatosis and inflammation plus either ballooning or at least stage 1a sinusoidal fibrosis. Informed consent.
Exclusion criteria	More than 3 drinks/day (10 g alcohol/drink) for the previous 5 years, cirrhosis, decompensated liver disease with ascites, encephalopathy or visceral haemorrhage, serum ALT >300 IU/L, pregnancy or lactation at the time of screening, serum creatinine >2 mg/dL, symptomatic coronary peripheral or neurovascular disease, symptomatic heart failure of New York Heart Association class 2 or higher, electrocardiogram with a QTc >450 milliseconds for males and >470 milliseconds for females, respiratory disease requiring oxygen therapy, and a history of cerebral or retinal haemorrhage

	or known bleeding diatheses. Subjects who had previously had bariatric surgery, >10% change in weight in the 2 months before entry or with a blood alcohol >0.02% at entry, possible drug-induced steatohepatitis (e.g. amiodarone or tamoxifen steatohepatitis), received therapy with non-stable dosage of agents which could potentially benefit NASH within the previous 6 months prior to the baseline liver biopsy, those who consumed vitamin E >60 IU/d, thiazolidinedione's, and n-3 PUFA >200 mg/d for more than 2 weeks within the 3 months before the qualifying chronic liver biopsy. Presence of other concomitant chronic liver diseases e.g. hepatitis C, hepatitis B surface antigen-positive hepatitis B, Wilson disease, a1 antitrypsin deficiency, and autoimmune hepatitis. Poorly controlled type 2 diabetes (haemoglobin A1C >9%) and those who had participated in an intervention trial within 3 months before entry into this study.
Age, gender and ethnicity	Age - Mean (SD): Placebo: 50.5 (12.5), EPA-E 1800: 47.8 (12.5), EPA-E 2700: 47.8 (11.1). Gender (M:F): Placebo: 42.7/57.3%, EPA-E 1800: 41.5/58.5%, EPA-E 2700: 33.7/66.3%. Ethnicity: Majority Caucasian
Further population details	
Extra comments	Baseline characteristics: BMI, mean (SD) placebo: 33.6 (5.9), EPA-E 1800: 35, EPA-E 2700: 35 (6.3); Type 2 diabetes (%) placebo: 30.7, EPA-E 1800: 42.7, EPA-E 2700: 31.4; AST (IU/L) placebo: 54 (39, 76), EPA-E 1800: 50.5 (37, 83), EPA-E 2700: 39, 80); ALT (IU/L) placebo: 79 (56, 118), EPA-E 1800: 77 (49, 109), EPA-E 2700: 76 (53, 118); fibrosis stage median (25th, 75th percentiles) placebo: 3.8 (1.9, 6.8), EPA-E 1800: 4.2 (2.5, 8.1), EPA-E 2700 4.3 (2.4, 8.1). Steatosis baseline values- median (25th, 75th percentile) placebo: 2 (1,2), EPA 1800: 2 (2, 2.25), EPA-E 2700: 2 (1.75, 3)
Indirectness of population	No indirectness
Interventions	(n=82) Intervention 1: Dietary supplements - Omega fatty acids. Ethyleicosapentanoic acid (EPA-E) 3 times a day to give a dosage of 1800 mg/d. Duration 12 months. Concurrent medication/care: People with type 2 diabetes or impaired glucose tolerance were allowed to participate if they were on a stable dosage of insulin, metformin, sulfonylurea, a-glucosidase inhibitor (acarbose), dipeptidyl-peptidase-4 inhibitors, or phenylalanine derivatives for the previous 6 months prior to the qualifying liver biopsy. (n=86) Intervention 2: Dietary supplements - Omega fatty acids. Ethyleicosapentanoic acid (EPA-E) 3 times a day to give a dosage of 2700 mg/d. Duration 12 months. Concurrent medication/care: People with type 2 diabetes or impaired glucose tolerance were allowed to participate if they were on a stable dosage of insulin, metformin, sulfonylurea, a-glucosidase inhibitor (acarbose), dipeptidyl-peptidase-4 inhibitors, or phenylalanine derivatives for the previous 6 months prior to the qualifying liver biopsy. (n=75) Intervention 3: Placebo / active control - Placebo. Placebo. Duration 12 months. Concurrent medication/care: People with type 2 diabetes or impaired glucose tolerance were allowed to participate if they were on a stable dosage of insulin, metformin, sulfonylurea, a-glucosidase inhibitor (acarbose), dipeptidyl-peptidase-4 inhibitors, or phenylalanine derivatives for the previous 6 months prior to the qualifying liver biopsy.

Funding	Equipment / drugs provided by industry (Supported by Mochida pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA FATTY ACIDS (EPA-E 1800) versus PLACEBO*

Protocol outcome 1: NAFLD progression with NAFLD fibrosis score at ≥12 months
- Actual outcome for Adults (18 years and over): NAS at 12 months; Other: Median; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months
- Actual outcome for Adults (18 years and over): AST levels at 12 months; Other: Median; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults (18 years and over): ALT levels at 12 months; Other: Median; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Weight loss at ≥12 months
- Actual outcome for Adults (18 years and over): Body weight (kg) at 12 months; Other: Median; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater
- Actual outcome for Adults (18 years and over): Proportion of responders: NAS ≤3 with fibrosis unchanged or NAS ≥2 with fibrosis unchanged at 12 months; Group 1: 20/55, Group 2: 22/55; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater
- Actual outcome for Adults (18 years and over): Proportion meeting criteria: NAS ≤3 with fibrosis unchanged at 12 months; Group 1: 18/55, Group 2: 20/55; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater
- Actual outcome for Adults (18 years and over): Proportion meeting criteria: NAS ≥2 with fibrosis unchanged at 12 months; Group 1: 15/55, Group 2: 18/55; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Any adverse event at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Any adverse events at 12 months; Group 1: 65/82, Group 2: 71/75; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 8: Serious adverse event at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Serious adverse events at 12 months; Group 1: 15/82, Group 2: 7/75; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 9: Severe adverse event at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Severe adverse events at 12 months; Group 1: 8/82, Group 2: 4/75; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA FATTY ACIDS (EPA-E 2700) versus PLACEBO*

Protocol outcome 1: NAFLD progression with NAFLD fibrosis score at ≥12 months
- Actual outcome for Adults (18 years and over): NAS at 12 months; Other: Median; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months
- Actual outcome for Adults (18 years and over): AST levels at 12 months; Other: Median; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults (18 years and over): ALT levels at 12 months; Other: Median; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Weight loss at ≥12 months
- Actual outcome for Adults (18 years and over): Body weight (kg) at 12 months; Other: Median; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater
- Actual outcome for Adults (18 years and over): Proportion of responders: NAS ≤3 with fibrosis unchanged or NAS ≥2 with fibrosis unchanged at 12 months; Group 1: 23/64, Group 2: 22/55; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater
- Actual outcome for Adults (18 years and over): Proportion meeting criteria: NAS ≤3 with fibrosis unchanged at 12 months; Group 1: 20/64, Group 2: 20/55; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater
- Actual outcome for Adults (18 years and over): Proportion meeting criteria: NAS ≥2 with fibrosis unchanged at 12 months; Group 1: 19/64, Group 2: 18/55; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Any adverse event at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Any adverse events at 12 months; Group 1: 74/86, Group 2: 71/75; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 8: Serious adverse event at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Serious adverse events at 12 months; Group 1: 5/86, Group 2: 4/75; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 9: Severe adverse event at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): Severe adverse events at 12 months; Group 1: 8/86, Group 2: 7/75; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months
* doses were combined for the review analysis.	

Study (subsidiary papers)	**Scorletti 2014[854] (Scorletti 2014[853])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=103)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Minimum 15 months, maximum 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Histological confirmation by liver biopsy, imaging evidence by MRS, ultrasound or CT

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) histological confirmation of NAFLD or (2) imaging evidence of liver fat (ultrasound, MRI or CT.
Exclusion criteria	Alcohol consumption >35 units (1 unit is 7.9 g of alcohol) per week for women and >50 units per week for men, pregnancy, breastfeeding, and hypersensitivity to DHA1EPA, soya, or the excipients.
Recruitment/selection of patients	Recruited between Jan 2010 and June 2011 from secondary care clinics held in 6 hospitals in the South of England
Age, gender and ethnicity	Age - Mean (SD): DHA+EPA (Omacor) group 46.8 (11.1) years, placebo group 54.0 (9.6) years. Gender (M:F): DHA+EPA (Omacor) group 25/26, placebo group 35/17. Ethnicity: Not reported
Further population details	
Extra comments	. Placebo versus DHA+EPA (Omacor) group, mean (SD); BMI (kg/m2) 32.0 (4.3) versus 34.3 (5.8), Weight (kg) 93 (14.4) versus 97 (17), ALT (U/l) 56.0 (34) versus 54.0 (43), AST (U/l) 41.5 (19) versus 38.0 (24), MRS liver fat (%) 21.7 (19.3) versus 23.0 (36.2), NAFLD fibrosis score 21.7 (1.3) versus 21.5 (1.4), Liver fibrosis score 9.0 (0.8) versus 8.8 (0.8). Placebo versus DHA+EPA (Omacor) group,(%); Diabetes (%) 9.0 versus 9.0.
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Dietary supplements - Omega fatty acids. Omacor (DHA+EPA) 4 g per day (1 g of Omacor contains 460 mg of EPA and 380 mg of DHA as ethyl esters). Duration 15 to 18 months. Concurrent medication/care: Not reported (n=52) Intervention 2: Placebo / active control - Placebo. 4 g per day of placebo olive oil (1 g of olive oil contains 600 mg of oleic acid plus lesser amounts of linoleic, palmitic, stearic, and alpha-linolenic acids). Duration 15 to 18 months. Concurrent medication/care: Not reported
Funding	Academic or government funding (National Institute of Health Research, Diabetes UK, Parnell Diabetes Trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA FATTY ACIDS versus PLACEBO

Protocol outcome 1: NAFLD progression with MRI / MRS at ≥12 months
- Actual outcome: MRS liver fat at 15 to 18 months; Group 1: mean 16.3 % (SD 22); n=46, Group 2: mean 19.7 % (SD 18); n=45; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: NAFLD progression with NAFLD fibrosis score at ≥12 months

- Actual outcome: NAFLD fibrosis score at 15 to 18 months; Group 1: mean -1.7 (SD 1.5); n=47, Group 2: mean -0.8 (SD 1.2); n=48; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months - Actual outcome: ALT at 15 to 18 months; Group 1: mean 44 U/l (SD 34); n=47, Group 2: mean 48.5 U/l (SD 25); n=45; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: AST at 15 to 18 months; Group 1: mean 30 U/l (SD 27); n=47, Group 2: mean 35 U/l (SD 17); n=48; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months
Study	Spadaro 2008[907]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy; Setting: Primary care

Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis of NAFLD was established on the basis of the following features: an increase in alanine aminotransferase (ALT) levels for ≥6 months before the study, ultrasonography demonstrating fatty liver, negative diagnostic tests for viral hepatitis (completely negative hepatitis B and C serologies for current or past exposure), absence of features of autoimmunity, absence of alcohol-induced nature of the disease (as established by clinical interview of the patients) and absence of other causes of liver diseases (drugs, toxin, metabolic)
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	An increase in alanine aminotransferase (ALT) levels for ≥6 months before the study, ultrasonography demonstrating fatty liver, negative diagnostic tests for viral hepatitis (completely negative hepatitis B and C serologies for current or past exposure), absence of features of autoimmunity, absence of alcohol-induced nature of the disease (as established by clinical interview of the patients) and absence of other causes of liver diseases (drugs, toxin, metabolic).
Exclusion criteria	Previous omega 3 fatty acids therapy within three months of study enrollment, known disease with increased proinflammatory cytokine levels (inflammatory bowel disease, autoimmune disease), known malignant neoplasm and pregnancy.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Usual care; 51.3 (9.8) omega 3 fatty acids; 50.16 (12.9) years. Gender (M:F): 19:17. Ethnicity: Not stated
Further population details	
Extra comments	. Omega 3 fatty acids versus control group, mean (SD); BMI (kg/m2) 30.1 (4.7) versus 31.0 (3.4), ALT (U/l) 56.6 (24.1) versus 59.7 (31.0), AST (U/l) 31.5 (13.2) versus 26.7 (8.8), ultrasound Doppler perfusion index 0.13 (0.05) versus 0.13 (0.05).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Dietary supplements - Omega fatty acids. Polyunsaturated fatty acid 2 g/day. Duration 6 months. Concurrent medication/care: AHA recommended diet (n=20) Intervention 2: No intervention / standard care - Standard care. AHA recommended diet. Duration 6 months. Concurrent medication/care: Not stated

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA FATTY ACIDS versus STANDARD CARE Protocol outcome 1: NAFLD progression with ultrasound at >3 months to < 6 months - Actual outcome for Adults (18 years and over): Ultrasound (range 0 to 3) at 6 months; Group 1: mean 1.278 IU/L (SD 1.127); n=18, Group 2: mean 2.2778 IU/L (SD 0.669); n=18; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months - Actual outcome for Adults (18 years and over): ALT at 6 months; Group 1: mean 39.5 U/l (SD 14); n=18, Group 2: mean 55.5 U/l (SD 31); n=18; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults (18 years and over): AST at 6 months; Group 1: mean 28 IU/L (SD 8.8); n=18, Group 2: mean 27.8 IU/L (SD 8.4); n=18; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	Vajro 2011[989]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Italy; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Liver ultrasound and liver enzyme tests
Stratum	Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined)
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	BMI >95th percentile for age and sex, persistent (>3 months) liver abnormalities (ALT levels >40 U/L) associated with ultrasonographic liver brightness, failed to adhere to previous slimming diets and not undergone any previous pharmacological treatments for obesity.
Exclusion criteria	Coexistence of causes of increased transaminase levels other than obesity which were investigated by appropriate biochemical tests or verified by anamnestic data, and receiving concomitant antibiotic treatment.
Age, gender and ethnicity	Age - Mean (SD): 10.7 (2.1). Gender (M:F): 18/2. Ethnicity: Not stated
Further population details	
Extra comments	. Baseline characteristics- mean (SD): Weight (kg) 61.7 (12.7), BMI 2.2 (0.27), ALT 66.9 (27.3), hepatorenal ultrasound ratio 1.24 (0.21).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Dietary supplements - Lactobacillus. Lactobacillus GG (12 billion CFU/day). Duration 8 weeks. Concurrent medication/care: Not stated (n=10) Intervention 2: Placebo / active control - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: Not stated
Funding	Academic or government funding (Italian ministry of university and research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTOBACILLUS versus PLACEBO Protocol outcome 1: Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months - Actual outcome for Children (younger than 11 years): ALT levels at 8 weeks; Group 1: mean 40.1 IU/L (SD 22.37); n=10, Group 2: mean 61.6 IU/L (SD 31.8); n=10; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at 3 months or greater; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

Study	**Wong 2013[1044]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)

Countries and setting	Conducted in Hong Kong (China); Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Liver biopsy
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-70 years; histology-proven NASH 6 months before inclusion; ALT >30 U/l in men and >19 U/l in women.
Exclusion criteria	Positive hepatitis B surface antigen; antibody against hepatitis C virus; anti-nuclear antibody titre >1/160; alcohol consumption >20g/day for men or >10 g/day for women; ALT >10 x upper limit of normal liver decompensation or malignancy; corticosteroids or methotrexate in last 6 months.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Probiotic: 42 (9) years; usual care: 55 (9) years. Gender (M:F): 13:7. Ethnicity: Not stated
Further population details	
Extra comments	. Probiotics versus control group, mean (SD); BMI (kg/m2) 30.2 (5.0) versus 28.7 (5.7), ALT (U/l) 96 (75) versus 72 (30), AST (U/l) 50 (25) versus 38 (15).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Dietary supplements - Lactobacillus delbrueckii subsp. bulgaricus (Lactobacillus bulgaricus). Lactobacillus plantarum, L. bulgaricus, L. acidophilus, L. rhamnosus and Bifidobacterium bifidum; 1 x 10g sachet contained 200 million probiotic cultures and 3g fructo-oligosaccharides (prebiotics), cellulose, magnesium stearate, silica and milk; 1 sachet twice a day. Duration 6 months. Concurrent medication/care: Lifestyle advice: lose weight, reduce fat intake and exercise at least 3 times per week (n=10) Intervention 2: No intervention / standard care - Standard care. Lifestyle advice: lose weight, reduce fat intake and exercise at least 3 times per week. Duration 6 months. Concurrent medication/care: Not stated
Funding	Academic or government funding (The Chinese University of Hong Kong)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTOBACILLUS DELBRUECKII SUBSP. BULGARICUS (LACTOBACILLUS BULGARICUS) versus STANDARD CARE

Protocol outcome 1: Liver function tests (for example ALT levels, ALT/AST levels) at 6 months to < 12 months - Actual outcome for Adults (18 years and over): ALT at 6 months; Group 1: mean -26 U/l (SD 91); n=10, Group 2: mean 2 U/l (SD 41); n=10; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults (18 years and over): AST at 6 months; Group 1: mean -13 U/l (SD 31); n=10, Group 2: mean 23 U/l (SD 32); n=10; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: NAFLD progression with MRI / MRS at ≥12 months - Actual outcome for Adults (18 years and over): MRS hepatic triglyceride content at 6 months; Group 1: mean -7.7 (SD 0.98); n=10, Group 2: mean -0.9 (SD 4.9); n=10; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Any adverse event at 3 months or greater - Actual outcome for Adults (18 years and over): All adverse events at 6 months; Group 1: 0/10, Group 2: 0/10; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; Hospitalisation at >3 months; NAFLD progression with liver biopsy at ≥12 months; NAFLD progression with MRI / MRS at ≥12 months; NAFLD progression with ultrasound at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at >3 months to <6months; NAFLD progression with NAFLD fibrosis score at ≥12 months; Weight loss at >3 months and < 6 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥12 months; NAFLD progression with NAFLD fibrosis score at ≥12 months; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at 6 months to <12 months; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with liver biopsy at >3 months to <6 months; NAFLD progression with ultrasound at 6 months to <12 months; NAFLD progression with ultrasound at >3 months to < 6 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Liver function tests (for example ALT levels, ALT/AST ratio) at ≥12 months; Quality of life at ≥12 months; Quality of life at ≥12 months; Weight loss at ≥12 months; Weight loss at ≥3 months to <12 months; NAFLD progression with MRI / MRS at >3 months to < 6 months; NAFLD progression with liver biopsy Composite of NAS ≤3/fibrosis unchanged or decrease NAS ≥2 fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy NAS ≤3/fibrosis unchanged at 3 months and greater; NAFLD progression with liver biopsy decrease NAS ≥2 fibrosis unchanged at 3 months and greater; Any adverse event at Greater or equal to 3 months; Serious adverse event at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Severe adverse events at 3 months or greater; Serious adverse event at 3 months or greater; Weight (kg) at ≥3 months to <12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; Length of stay at >3 months

H.7 Exercise interventions

Study	Eckard 2013[269]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Living in study are at least 9 months, liver biopsy confirmed NAFLD 6 months prior to start of study.
Exclusion criteria	Alcohol consumption >20 g/day, viral hepatitis, chronic liver disease of unknown etiology, inborn errors of metabolism, insulin therapy, pregnancy.
Recruitment/selection of patients	Open recruitment Oct 2008 to Feb 2010.
Age, gender and ethnicity	Age - Mean (SD): 50 (11). Gender (M:F): 61%/49%. Ethnicity: Not reported
Further population details	
Extra comments	Baseline characteristics exercise versus control mean (SD); BMI (kg/m2) 31.3(4.4) versus 35.3(3.5), weight (lbs) 197.4(34.6) versus 224.9(39.3), ALT (U/l) 79.9 (55.5) versus 48.3 (46.6), AST (U/l) 55.6 (43.3) versus 36.5 (26.7)
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Exercise - Aerobic exercise / cardio-exercise. 20-60 min 4 to 7 days/week, 18 step program including warm up, exercise bike, walking on treadmill, various arm and leg stretches, and gradual cool-down with exercise ramped up over 6 weeks. Duration 6 months. Concurrent medication/care: Standard care and dietitian support (n=11) Intervention 2: Control - Usual care. Standard care. Duration 6 months. Concurrent medication/care: 1 hour

	session with dietitian
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AEROBIC EXERCISE / CARDIO-EXERCISE versus USUAL CARE Protocol outcome 1: NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): Liver biopsy NAFLD activity score at 6 months; Group 1: mean 2.9 (SD 1.4); n=9, Group 2: mean 3.3 (SD 1.6); n=11; NAFLD activity score 0-8 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function test ALT at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): ALT at 6 months; Group 1: mean -21.8 IU/l (SD 30.6); n=9, Group 2: mean -4.3 IU/l (SD 38.7); n=11; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function test AST at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): AST at 6 months; Group 1: mean -8.4 IU/l (SD 10.4); n=9, Group 2: mean -2.9 IU/l (SD 25.8); n=11; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; NAFLD progression with MRI / MRS at 12 months and greater; NAFLD progression with ultrasound at 12 months and greater; Liver function test AST/ALT ratio at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to 12 months; NAFLD progression with fibroscan/ transient elastography at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function test AST/ALT ratio) at 12 months and greater; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with ultrasound at ≥3 months to <12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 12 months and greater; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Quality of life at 6 months to <12 months; Quality of life at 12 months and greater; NAFLD progression with MRI / MRS at ≥3 months to <12 months; Liver function test ALT at 12 months and greater; Liver function test AST at 12 months and greater; Weight at ≥3 months to <12 months; Weight at 12 months and greater; NAFLD progression with liver biopsy at 12 months and greater

Study (subsidiary papers)	Hallsworth 2011[383] (Hallsworth 2011[381], Hallsworth 2011[380])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=21)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: NAFLD fibrosis scoring system
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Sedentary adults with clinically defined non-advanced NAFLD defined as greater than 5% IHL and a score of less than −1.445 on the NAFLD fibrosis scoring system, people with type 2 diabetes mellitus, diet and metformin were acceptable for inclusion if stable for 6 months. Sedentary prior to study start (≤60 min vigorous activity per week).
Exclusion criteria	Heart or kidney disease, implanted ferrous metal, pre-existing medical conditions preventing participation in exercise programme, insulin sensitising treatment or dietary change, alcohol intake above 21 units for men or 14 units for women. Subjects would be excluded from analysis if body weight changed more than 2.5% from baseline during the study as this could have independent effect on IHL.
Recruitment/selection of patients	Screened for NAFLD
Age, gender and ethnicity	Age - Mean (SD): Exercise group 52 (13.3) years, control 62 (7.4) years. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	
Extra comments	Baseline characteristics, exercise versus control mean (SD); BMI (kg/m2) 32.3 (4.9) versus 32.3 (4.9), weight (kg) 96.1 (10.9) versus 94.0 (12.0), ALT (U/l) 59.6 (38.6) versus 61.6 (41.4)
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Exercise - Resistance exercise / repeated muscle contraction – strength, anaerobic endurance. Resistance exercise performed three times per week on non-consecutive days for 8 weeks. Programme consisted of 8 exercises: biceps curl; calf raise; triceps press; chest press; seated hamstrings curl; shoulder press; leg extension and lateral pull down. Each session lasted between 45 and 60 min and consisted of 10 min warm-up at approximately 60% maximum heart rate on a cycle ergometer followed by resistance exercise done as a circuit, ending with a repeat of the warm-up. Initially, participants did two circuits using 50% of their one repetition maximum, progressing to three

	circuits, using a minimum 70% of their one repetition maximum by week 7. Participants encouraged to increase the resistance used each week. Duration 8 weeks. Concurrent medication/care: Biweekly supervised exercise sessions used to encourage adherence and progression and to resolve any problems (n=10) Intervention 2: Control - Usual care. Standard care. Duration 8 weeks. Concurrent medication/care: Not reported
Funding	Academic or government funding (European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no Health-F2-2009-241762, for the project FLIP; the Medical Research Council; the UK National Institute for Health Research Biomedical Research Centre on Ageing and Age-Related Diseases and Diabetes UK)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESISTANCE EXERCISE / REPEATED MUSCLE CONTRACTION – STRENGTH, ANAEROBIC ENDURANCE versus USUAL CARE Protocol outcome 1: NAFLD progression with MRI / MRS at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): 1H-MRS intrahepatic lipid at 8 weeks; Group 1: mean 12.2 % (SD 9); n=11, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function test ALT at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): Metabolic test ALT at 8 weeks; Group 1: mean 59.6 U/l (SD 39); n=11, Group 2: mean 61.4 U/l (SD 44); n=8; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Weight at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): Weight (kg) at 8 weeks; Group 1: mean 96.1 kg (SD 10.5); n=11, Group 2: mean 94.6 kg (SD 10.7); n=8; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; NAFLD progression with MRI / MRS at 12 months and greater; NAFLD progression with ultrasound at 12 months and greater; Liver function test AST/ALT ratio at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to 12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function test AST/ALT ratio) at 12 months and greater; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with ultrasound at ≥3 months to <12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 12 months and greater; NAFLD progression with

	Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Quality of life at 6 months to <12 months; Quality of life at 12 months and greater; Liver function test ALT at 12 months and greater; Liver function test AST at 12 months and greater; Liver function test AST at ≥3 months to <12 months; Weight at 12 months and greater; NAFLD progression with liver biopsy at 12 months and greater

Study	**Pugh 2013[788]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=13)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ALT levels >41 U/l for at least 6 months in the presence of an echobright liver on abdominal ultrasonography
Stratum	Adults (18 years and over)
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	NAFLD (ALT levels >41 U/l for at least 6 months), sedentary nonsmokers with no history of type 2 diabetes or excessive alcohol intake (average weekly consumption of <14 units for females and <21 units for males).
Exclusion criteria	Other forms of liver disease caused by hepatitis B or C, autoimmune hepatitis, primary biliary cirrhosis and other metabolic liver disease. Ischaemic heart disease or contraindications to exercise.
Age, gender and ethnicity	Age - Other: Mean (95% CIs) Exercise group 50 (44,56), control group 48 (38,57) years. Gender (M:F): 7/6. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics-mean (95% CIs): BMI (kg/m2) exercise group 31 (29, 33), control group 30 (26, 34), Weight (kg) exercise group 88.6 (81, 96.3), control group 84.4 (74.6, 94.1).. Baseline characteristics, exercise versus control mean (95% CI); BMI (kg/m2) 31 (29 to 32) versus 30 (25 to 35), weight (kg) 93 (82 to 104) versus 84 (63 to 105), ALT (U/l) 60 (35 to 105) versus 69 (36 to 132), AST (U/l) 38 (24 to 63) versus 47 (27 to 80)
Indirectness of population	No indirectness
Interventions	(n=7) Intervention 1: Exercise - Aerobic exercise / cardio-exercise. 3 times a week of supervised moderate-intensity

	aerobic exercise training for 30 minutes, increased to 5 times a week after week 12 . Duration 16 weeks. Concurrent medication/care: 3 of the NAFLD patients were taking antihypertensive medication (n=6) Intervention 2: Control - Usual care. Advised by hepatologist or clinical nurse to modify lifestyle by losing weight and remaining active. Duration 16 week. Concurrent medication/care: None
Funding	Academic or government funding (European foundation for the study of diabetes)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AEROBIC EXERCISE / CARDIO-EXERCISE versus USUAL CARE Protocol outcome 1: NAFLD progression with MRI / MRS at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): 1H-MRS intrahepatic lipid CH2-water (%) at 16 weeks; Group 1: mean -13 % (SD 5.4765); n=5, Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function test ALT at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): ALT U/l at 16 weeks; Mean ; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function test AST at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): AST U/l at 16 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Weight at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): Weight (kg) at 16 weeks; Mean ; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; NAFLD progression with MRI / MRS at 12 months and greater; NAFLD progression with ultrasound at 12 months and greater; Liver function test AST/ALT ratio at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to 12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function test AST/ALT ratio) at 12 months and greater; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with ultrasound at ≥3 months to <12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 12 months and greater; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Quality of life at 6 months to <12 months; Quality of life at 12 months and greater; Liver function test ALT at 12 months and greater; Liver function test AST at 12 months and greater; Weight at 12 months and greater; NAFLD progression with liver biopsy at 12 months and greater

Study (subsidiary papers)	Sullivan 2012[925] (Sullivan 2011[924])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=18)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: IHTG content >10%
Stratum	Adults (18 years and over)
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Obesity, NAFLD (IHTG content >10%), weight stable (<3% change in self-reported weight for at least 3 months before the study), sedentary (<1 hour of self-reported exercise per week).
Exclusion criteria	Chronic liver disease other than NAFLD, Michigan alcohol screening test score >4, diabetes, plasma TG concentration >400 mg/dL.
Age, gender and ethnicity	Age - Other: Not stated. Gender (M:F): 5/13. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics, mean (SEM): BMI (BMI (kg/m2) control group 40 (2.2), exercise group 37.1 (1.1), Body mass (kg) control group 113.7 (6), exercise group 103.1 (4.2).. Baseline characteristics, exercise versus control mean (SD); BMI (kg/m2) 37.1 (1.1) versus 40.0 (2.2), weight (kg) 103.1 (4.2) versus 113.7 (6.0), ALT (U/l) 45.6 (8.6) versus 33.7 (6.0)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Exercise - Aerobic exercise / cardio-exercise. Aerobic exercise 30-60 minutes, 5 times per week at 45-55% of their VO2 peak. Once a week the exercise was under supervision at a exercise facility, other 4 sessions completed at home. Duration 16 weeks. Concurrent medication/care: Not stated (n=9) Intervention 2: Control - Usual care. Control group continued activities of daily living as per normal. Duration 16 weeks. Concurrent medication/care: Not stated

Funding	Academic or government funding (NIH grants, USA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AEROBIC EXERCISE / CARDIO-EXERCISE versus USUAL CARE

Protocol outcome 1: NAFLD progression with MRI / MRS at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): MRS intrahepatic triglyceride at 16 weeks; Group 1: mean 17 % (SD 8.2916); n=11, Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function test ALT at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): ALT (U/l) at 16 weeks; Group 1: mean 39.3 IU/L (SD 7.4); n=12, Group 2: mean 39.9 IU/L (SD 9.2); n=6; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Weight at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): Body mass at 16 weeks; Group 1: mean 102.9 kg (SD 4.2); n=12, Group 2: mean 113.9 kg (SD 5.7); n=6; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; NAFLD progression with MRI / MRS at 12 months and greater; NAFLD progression with ultrasound at 12 months and greater; Liver function test AST/ALT ratio at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to 12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function test AST/ALT ratio) at 12 months and greater; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with ultrasound at ≥3 months to <12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 12 months and greater; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Quality of life at 6 months to <12 months; Quality of life at 12 months and greater; Liver function test ALT at 12 months and greater; Liver function test AST at 12 months and greater; Liver function test AST at ≥3 months to <12 months; Weight at 12 months and greater; NAFLD progression with liver biopsy at 12 months and greater

Study (subsidiary papers)	**Thoma 2013[958] (Thoma 2013[959])**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=29)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: >5% liver fat and NAFLD fibrosis score maximum of ≤-1.455
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Sedentary adults ≤60 minutes moderate-vigorous activity per week, with clinically defined non-advanced NAFLD.
Exclusion criteria	Inability to give informed consent, heart or kidney disease, viral hepatitis, uncontrolled thyroid conditions, hemochromatosis, suspicion of drug related steatosis, implanted ferrous material, pre-existing medical conditions preventing participation in the exercise program, medication for type 2 diabetes other than metformin and self-reported weekly intake above 21 units for men or 14 units for women.
Age, gender and ethnicity	Age - Mean (SD): Control group: 52 (12), high intensity training (HIT) group: 54 (10). Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics, mean (SD): BMI (kg/m2): control group 31 (5), HIT group 31 (4); Weight (kg): control group 90 (11), HIT group 90 (14). Baseline characteristics, exercise versus control mean (SD); BMI (kg/m2) 31 (4) versus 31 (5), weight (kg) 90 (14) versus 90 (11), ALT (U/l) 52 (29) versus 47 (22), AST (U/l) 36 (18) versus 31 (8)
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Exercise - High intensity training – alternate intense anaerobic and recover. Cycle ergometer-based HIT protocol completed three times a week on non-consecutive days at a commercial fitness facility following audio instructions. First two sessions were supervised, participants kept an exercise diary to assess adherence for the rest of the intervention period. The intervals of cycling became longer every week and the recovery periods consisted of 90 seconds passive recovery and 60 seconds band resisted upper body exercise. . Duration 12 weeks. Concurrent medication/care: Participants asked to retain their diet and maintain their body weight within 1% of baseline (n=14) Intervention 2: Control - Usual care. Continuing any prescription medication and going for regular monitoring of their condition(s) with their normal GP and/or consultant(s). . Duration 12 weeks. Concurrent medication/care: Maintain their body weight

Funding	Academic or government funding (European Union seventh Framework Programme, Medical research council, NIHR Biomedical Research Centre on Ageing and Age Related Diseases, and Diabetes UK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH INTENSITY TRAINING – ALTERNATE INTENSE ANAEROBIC AND RECOVER versus USUAL CARE

Protocol outcome 1: NAFLD progression with MRI / MRS at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): 1H-MRS intrahepatic lipid at 12 weeks; Group 1: mean 7.8 % (SD 2.4); n=12, Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function test ALT at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): ALT levels (U/l) at 12 weeks; Group 1: mean 51 U/l (SD 24); n=12, Group 2: mean 42 U/l (SD 20); n=11; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Liver function test AST at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): AST levels (U/l) at 12 weeks; Group 1: mean 33 U/l (SD 15); n=12, Group 2: mean 35 U/l (SD 8); n=11; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): Weight (kg) at 12 weeks; Group 1: mean 88.5 kg (SD 13.5); n=12, Group 2: mean 90.1 kg (SD 10); n=11; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; NAFLD progression with MRI / MRS at 12 months and greater; NAFLD progression with ultrasound at 12 months and greater; Liver function test AST/ALT ratio at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to 12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function test AST/ALT ratio) at 12 months and greater; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with ultrasound at ≥3 months to <12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 12 months and greater; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Quality of life at 6 months to <12 months; Quality of life at 12 months and greater; Liver function test ALT at 12 months and greater; Liver function test AST at 12 months and greater; Weight at 12 months and greater; NAFLD progression with liver biopsy at 12 months and greater

Study (subsidiary papers)	Zelber-sagi 2014[1084] (Zelber-sagi 2012[1082])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Israel
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ultrasound
Stratum	Adults (18 years and over)
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Aged between 20-65 years, diagnosis of fatty liver by ultrasound in the past 6 months.
Exclusion criteria	Secondary liver disease including hepatitis B or C, excessive alcohol consumption (>30g/d for men and >20g/d for women), medication that may elevate ALT levels or lead to hepatic steatosis, known diabetes, major chronic diseases including renal, cardiovascular, lung, uncontrolled hypertension, inflammatory bowel disease, active cancer, autoimmune disorders and orthopedic contraindications for resistance training.
Age, gender and ethnicity	Age - Mean (SD): 46.47 (10.76) years. Gender (M:F): 34/30. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics Mean (SD):BMI (kg/m2) exercise group 30.75 (4.52), sham group 31.3 (4.14). Baseline characteristics, exercise versus control mean (SD); BMI (kg/m2) 30.75 (4.52) versus 31.301 (4.14), ALT (U/l) 53.00 (35.61) versus 50.13 (37.20), AST (U/l) 34.30 (17.49) versus 32.00 (14.76)
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Exercise - Resistance exercise / repeated muscle contraction – strength, anaerobic endurance. Resistance training performed in a community setting, 3 times a week, 40 minute sessions. Duration 3 months. Concurrent medication/care: Not stated (n=38) Intervention 2: Control - Sham. Home stretching routine lasting 20 minutes, 3 times a week. Duration 3 months. Concurrent medication/care: Not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESISTANCE EXERCISE / REPEATED MUSCLE CONTRACTION – STRENGTH, ANAEROBIC ENDURANCE versus SHAM Protocol outcome 1: Liver function test ALT at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): ALT (U/l) at 3 months; Group 1: mean -5.3 U/L (SD 9.65); n=33, Group 2: mean -5.1 U/L (SD 14.43); n=31; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function test AST at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): AST (U/l) at 3 months; Group 1: mean -2.76 U/L (SD 7.75); n=33, Group 2: mean -2.68 U/L (SD 6.95); n=31; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Weight at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): Weight (kg) at 3 months; Group 1: mean -0.39 kg (SD 1.43); n=33, Group 2: mean 0.33 kg (SD 1.21); n=31; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; NAFLD progression with MRI / MRS at 12 months and greater; NAFLD progression with ultrasound at 12 months and greater; Liver function test AST/ALT ratio at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to 12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function test AST/ALT ratio) at 12 months and greater; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with ultrasound at ≥3 months to <12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 12 months and greater; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Quality of life at 6 months to <12 months; Quality of life at 12 months and greater; NAFLD progression with MRI / MRS at ≥3 months to <12 months; Liver function test ALT at 12 months and greater; Liver function test AST at 12 months and greater; Weight at 12 months and greater; NAFLD progression with liver biopsy at 12 months and greater

Study (subsidiary papers)	**Zelber-sagi 2014[1084] (Zelber-sagi 2012[1082])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Israel

Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ultrasound
Stratum	Adults (18 years and over)
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Aged between 20-65 years, diagnosis of fatty liver by ultrasound in the past 6 months.
Exclusion criteria	Secondary liver disease including hepatitis B or C, excessive alcohol consumption (>30g/d for men and >20g/d for women), medication that may elevate ALT levels or lead to hepatic steatosis, known diabetes, major chronic diseases including renal, cardiovascular, lung, uncontrolled hypertension, inflammatory bowel disease, active cancer, autoimmune disorders and orthopedic contraindications for resistance training.
Age, gender and ethnicity	Age - Mean (SD): 46.47 (10.76) years. Gender (M:F): 34/30. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics Mean (SD):BMI (kg/m2) exercise group 30.75 (4.52), sham group 31.3 (4.14). Baseline characteristics, exercise versus control mean (SD); BMI (kg/m2) 30.75 (4.52) versus 31.301 (4.14), ALT (U/l) 53.00 (35.61) versus 50.13 (37.20), AST (U/l) 34.30 (17.49) versus 32.00 (14.76)
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Exercise - Resistance exercise / repeated muscle contraction – strength, anaerobic endurance. Resistance training performed in a community setting, 3 times a week, 40 minute sessions. Duration 3 months. Concurrent medication/care: Not stated (n=38) Intervention 2: Control - Sham. Home stretching routine lasting 20 minutes, 3 times a week. Duration 3 months. Concurrent medication/care: Not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESISTANCE EXERCISE / REPEATED MUSCLE CONTRACTION – STRENGTH, ANAEROBIC ENDURANCE versus SHAM

Protocol outcome 1: Liver function test ALT at ≥3 months to <12 months
- Actual outcome for Adults (18 years and over): ALT (U/l) at 3 months; Group 1: mean -5.3 U/L (SD 9.65); n=33, Group 2: mean -5.1 U/L (SD 14.43); n=31; Risk of bias:

Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function test AST at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): AST (U/l) at 3 months; Group 1: mean -2.76 U/L (SD 7.75); n=33, Group 2: mean -2.68 U/L (SD 6.95); n=31; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Weight at ≥3 months to <12 months - Actual outcome for Adults (18 years and over): Weight (kg) at 3 months; Group 1: mean -0.39 kg (SD 1.43); n=33, Group 2: mean 0.33 kg (SD 1.21); n=31; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 months to <12 months; NAFLD progression with MRI / MRS at 12 months and greater; NAFLD progression with ultrasound at 12 months and greater; Liver function test AST/ALT ratio at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at ≥3 months to 12 months; NAFLD progression with NAFLD fibrosis score at ≥3 months to <12 months; NAFLD progression with fibroscan/ transient elastography at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 12 months and greater; NAFLD progression with NAFLD fibrosis score at 6 months to <12 months; Liver function test AST/ALT ratio) at 12 months and greater; NAFLD progression with liver biopsy at ≥3 months to <12 months; NAFLD progression with ultrasound at ≥3 months to <12 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at 12 months and greater; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at ≥3 months to <12 months; Quality of life at 6 months to <12 months; Quality of life at 12 months and greater; NAFLD progression with MRI / MRS at ≥3 months to <12 months; Liver function test ALT at 12 months and greater; Liver function test AST at 12 months and greater; Weight at 12 months and greater; NAFLD progression with liver biopsy at 12 months and greater

H.8 Lifestyle modification

Study	**Al-Jiffri 2013[32]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Saudi Arabia; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elevated AST and/or ALT levels and liver biopsy
Stratum	Adults (18 years and over)

Study	Al-Jiffri 2013[32]
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Male patients with type 2 diabetes and NAFLD identified by elevated AST and/or ALT levels and liver biopsy showing steatosis in at least 10% of hepatocytes.
Exclusion criteria	Smoking, hypertension, other liver diseases, history of CVD, thyroid disease and orthopaedic problems inhibiting treadmill training.
Age, gender and ethnicity	Age - Mean (range): 30 to 55 years. Gender (M:F): 100% male. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics - mean (SD): ALT levels in control group 47.22 (6.05) and treatment group 46.88 (5.41), AST levels in control group 46.16 (6.87) and treatment group 45.98 (6.63), BMI ranging from 30 to 35 kg/m2
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Diet and exercise - Any diet with any exercise. Exercise: aerobic treadmill-based program was set to 65-75% of the maximum heart rate according to modified Bruce protocol. The program consisted of 5 minutes warm-up on the treadmill, 30 minutes training and 5 minutes cool down. Three time a week for three weeks .Diet: Interview-based food survey by dietician to specify previous food habits and possible anomalies to dietary behaviour, The prescribed low calories diet was balanced with 15% protein, 30-35% fat and 50-55% carbohydrate to give a total of 1200 kilocalories daily for 2 months. Duration 3 months. Concurrent medication/care: Not stated (n=50) Intervention 2: Diet - Lower percentage fat. Diet: Interview-based food survey by dietician to specify previous food habits and possible anomalies to dietary behaviour, The prescribed low calories diet was balanced with 15% protein, 30-35% fat and 50-55% carbohydrate to give a total of 1200 kilocalories daily for 2 months. . Duration 3 months. Concurrent medication/care: Not stated
Funding	Academic or government funding (Deanship of Scientific Research, King Abdulaziz University, Saudi Arabia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET WITH ANY EXERCISE versus LOWER PERCENTAGE FAT

Protocol outcome 1: Liver function tests - AST levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): AST levels at 3 months; Group 1: mean 34.36 U/L (SD 5.11); n=50, Group 2: mean 46.87 U/L (SD 7.24); n=50; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests - ALT levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): ALT levels at 3 months; Group 1: mean 33.28 U/L (SD 4.76); n=50, Group 2: mean 47.91 U/L (SD 6.75); n=50; Risk of

Study	Al-Jiffri 2013[32]
bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with liver biopsy at Greater or equal to 3 months; NAFLD progression with ultrasound at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; NAFLD progression with MRI / MRS at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Weight (kg) at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months

Study	Chen 2008[197]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=54)
Countries and setting	Conducted in Taiwan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Ultrasound
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Central obesity- an abdominal circumference of at least 90 cm for men and at least 80 cm for women or BMI (kg/m2) >25,, total cholesterol level of at least 200 mg/dL or triglyceride level of at least 150 mg/dL, high density lipoprotein cholesterol level of <40 mg/dL for men and <50 mg/dL for women and blood pressure of at least 130/ at least 85 mmHg or under treatment for hypertension.
Exclusion criteria	History of alcohol abuse or chronic intake (>1 drink/week confirmed by self-report questionnaire), diabetes, hepatitis B or C, hypothyroidism, anaemia, hyperlipidaemia, inability to participate in aerobic exercises due to adverse effects.
Age, gender and ethnicity	Age - Mean (SD): Control group 37.7 (6.6), exercise group 36 (6.9), diet and exercise group 40.1 (6.2) years. Gender (M:F): Control group 8/7, exercise group 16/7, diet and exercise group 10/6. Ethnicity: Not stated
Further population details	

Study	Chen 2008[197]
Extra comments	Baseline characteristics- mean (SD): body weight (kg) C group 84.2 (15.2), E group 85.3 (12.1) D+E group 83.3 (10.9), AST levels (U/l) C group 30.7 (14.7), E group 34.5 (13), D+E group 36.6 (18.8), ALT levels (U/l) C group 47.3 (30.1, E group 54 (29.4), E+D group 63.4 (49.2), severity of fatty liver on ultrasound C group 1.8 (0.7), E group 1.8 (0.7), D+E group 1.4 (0.5)
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Exercise - Aerobic exercise/ cardio-exercise. High intensity stationary bicycle program at a frequency of 1 hour twice a week. Duration 10 weeks. Concurrent medication/care: Not stated (n=15) Intervention 2: No intervention / control - No intervention. Control population, no detail given. Duration 10 weeks. Concurrent medication/care: Not stated (n=16) Intervention 3: Diet and exercise - Any diet with any exercise. Participants given guidance on a low-calorie balanced diet with a suggested daily calorie intake of 25 kcal/IBW, the range of daily calorie intake was 1,200-1,500 kcal. They also participated in a high-intensity stationary bicycle exercise program at a frequency of 1 hour twice a week for 10 weeks. They kept a record of a diet diary and monitored by a dietician. Exercises were performed under a professional instructor. . Duration 10 weeks. Concurrent medication/care: Not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET WITH ANY EXERCISE versus AEROBIC EXERCISE/ CARDIO-EXERCISE

Protocol outcome 1: Liver function tests - AST levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): AST (U/l) at 10 weeks; Group 1: mean 25.56 (SD 6.54); n=16, Group 2: mean 30.43 (SD 10.84); n=23; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests - ALT levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): ALT (U/l) at 10 weeks; Group 1: mean 34 (SD 18.84); n=16, Group 2: mean 44.78 (SD 23.78); n=23; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Weight (kg) at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Body weight (kg) at 10 weeks; Group 1: mean 78.05 (SD 10.59); n=16, Group 2: mean 83.9 (SD 15.72); n=23; Risk of bias: Very high; Indirectness of outcome: No indirectness

Study	Chen 2008[197]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET WITH ANY EXERCISE versus NO INTERVENTION Protocol outcome 1: Liver function tests - AST levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): AST (U/l) at 10 weeks; Group 1: mean 25.64 (SD 6.54); n=16, Group 2: mean 35 (SD 23.62); n=15; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests - ALT levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): ALT (U/l) at 10 weeks; Group 1: mean 34 (SD 18.84); n=16, Group 2: mean 44.27 (SD 22.45); n=15; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Weight (kg) at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): Body weight (kg) at 10 weeks; Group 1: mean 78.05 (SD 10.59); n=16, Group 2: mean 84.08 (SD 15.25); n=15; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with liver biopsy at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; NAFLD progression with MRI / MRS at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months

Study	Eckard 2013[269]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: liver biopsy
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable

Study	Eckard 2013[269]
Inclusion criteria	Living in study for at least 9 months, liver biopsy confirmed NAFLD 6 months prior to start of study.
Exclusion criteria	Alcohol consumption >20 g/day, viral hepatitis, chronic liver disease of unknown aetiology, inborn errors of metabolism, insulin therapy, pregnancy.
Recruitment/selection of patients	Open recruitment Oct 2008 to Feb 2010
Age, gender and ethnicity	Age - Mean (SD): 50 (11). Gender (M:F): 61/49%. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics mean (SD); BMI (kg/m2) Ex group 31.3(4.4) Con group 35.3(3.5) low fat diet and moderate exercise (LFDE) group 32.7 (4.7), moderate fat diet and moderate exercise (MFDE) group 40.3 (9.3), weight (lbs) Ex group 197.4(34.6) Con group 224.9(39.3) LFDE group 206.3 (38.4) MFDE group 234.5 (50.2). NAFLD activity score Ex group 3.9 (1.7) Con group 3.6 (1.1) LFDE group 3.9 (1.7) MDFE group 3.7 (1.1), ALT (U/l) Ex group 79.9 (55.5) Con group 48.3 (46.6) LFDE71.2 (39.8) MFDE group 70.3 (50.7), AST (U/l) Ex group 55.6 (43.3) Con group 36.5 (26.7) LFDE group 47 (23) MDFE group 55.6 (43.3)
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Diet and exercise - Any diet with any exercise. Low-fat diet and moderate exercise: attended specialised nutrition classes conducted by a registered dietician, given an individualised nutrition prescription, received education on an exercise program for weight loss, initial class was taught by an exercise physiologist who started each participant on an individualised exercise program. Duration 6 months. Concurrent medication/care: Not stated (n=11) Intervention 2: Diet and exercise - Any diet with any exercise. Moderate-fat/low-processed carbohydrate diet and moderate exercise: attended specialised nutrition classes conducted by a registered dietician, given an individualised nutrition prescription, received education on an exercise program for weight loss, initial class was taught by an exercise physiologist who started each participant on an individualised exercise program. Duration 6 months. Concurrent medication/care: Not stated (n=13) Intervention 3: Exercise - Aerobic exercise/ cardio-exercise. 20-60 minutes 4 to 7 days/week, 18 step program including warm-up, exercise bike, walking on treadmill, various arm and leg stretches and gradual cool down with exercise ramped over 6 weeks. Duration 6 months. Concurrent medication/care: Standard care and dietician support (n=14) Intervention 4: No intervention / control - Control. Standard care. Duration 6 months. Concurrent medication/care: 1 hour session with dietician

Study	Eckard 2013[269]
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET PLUS ANY EXERCISE PLUS (LFDE) versus AEROBIC EXERCISE/ CARDIO-EXERCISE

Protocol outcome 1: NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): NAS at 6 months; Group 1: mean -1.3 (SD 1.3); n=12, Group 2: mean -0.8 (SD 1.4); n=9; NAFLD activity score 0-8 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests - AST levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): AST levels (U/l) at 6 months ; Group 1: mean -15.9 (SD 19.1); n=12, Group 2: mean -8.4 (SD 10.4); n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Liver function tests - ALT levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): ALT levels (U/l) at 6 months; Group 1: mean -27.5 (SD 27.9); n=12, Group 2: mean -21.8 (SD 30.6); n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight (kg) at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Wight (lbs) at 6 months; Group 1: mean -0.2 (SD 5.4); n=12, Group 2: mean 0.1 (SD 4.8); n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET PLUS ANY EXERCISE PLUS (LFDE) versus USUAL CARE

Protocol outcome 1: NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): NAS at 6 months; Group 1: mean -1.3 (SD 1.3); n=12, Group 2: mean -0.4 (SD 1.5); n=11; NAFLD activity score 0-8 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests - AST levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): AST levels (U/l) at 6 months ; Group 1: mean -15.9 (SD 19.1); n=12, Group 2: mean -2.9 (SD 25.8); n=11; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Liver function tests - ALT levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): ALT levels (U/l) at 6 months; Group 1: mean -27.5 (SD 27.9); n=12, Group 2: mean -4.3 (SD 38.7); n=11; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Eckard 2013[269]
Protocol outcome 4: Weight (kg) at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): Wight (lbs) at 6 months; Group 1: mean -0.2 (SD 5.4); n=12, Group 2: mean -2.5 (SD 5.3); n=11; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET PLUS ANY EXERCISE PLUS (MFDE) versus AEROBIC EXERCISE/ CARDIO-EXERCISE Protocol outcome 1: NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): NAS at 6 months; Group 1: mean -1.2 (SD 1); n=9, Group 2: mean -0.8 (SD 1.4); n=9; NAFLD activity score 0-8 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests - AST levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): AST levels (U/l) at 6 months ; Group 1: mean -19.6 (SD 47.9); n=9, Group 2: mean -8.4 (SD 10.4); n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function tests - ALT levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): ALT levels (U/l) at 6 months; Group 1: mean -19.8 (SD 54.9); n=9, Group 2: mean -21.8 (SD 30.6); n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Weight (kg) at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): Wight (lbs) at 6 months; Group 1: mean -3 (SD 4.7); n=9, Group 2: mean 0.1 (SD 4.8); n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET PLUS ANY EXERCISE PLUS (MFDE) versus USUAL CARE Protocol outcome 1: NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): NAS at 6 months; Group 1: mean -1.2 (SD 1); n=9, Group 2: mean -0.4 (SD 1.5); n=11; NAFLD activity score 0-8 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests - AST levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): AST levels (U/l) at 6 months ; Group 1: mean -19.6 (SD 47.9); n=9, Group 2: mean -2.9 (SD 25.8); n=11; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function tests - ALT levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): ALT levels (U/l) at 6 months; Group 1: mean -19.8 (SD 54.9); n=9, Group 2: mean -4.3 (SD 38.7); n=11; Risk of bias: High; Indirectness of outcome: No indirectness	

Study	Eckard 2013[269]
Protocol outcome 4: Weight (kg) at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): Wight (lbs) at 6 months; Group 1: mean -3 (SD 4.7); n=9, Group 2: mean -2.5 (SD 5.3); n=11; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with liver biopsy at Greater or equal to 3 months; NAFLD progression with ultrasound at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; NAFLD progression with MRI / MRS at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months

Study	Promrat 2010[786]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention time: 48 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: liver biopsy
Stratum	Adults (18 years and over)
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values (ALT > 41 or AST > 34 U/L), body mass index (BMI) between 25 and 40 kg/m2, and no evidence of another form of liver disease. All participants were required to complete a 2-week run-in period consisting of completion of self-monitoring records of diet and exercise.
Exclusion criteria	Significant alcohol consumption (>1 standard drink per day), contraindications to obtaining a liver biopsy, inability to walk 2 blocks or a quarter of a mile without stopping, pregnancy, engagement in an active weight loss program or taking weight-loss medication, substance abuse, and significant psychiatric problems.
Age, gender and ethnicity	Age - Mean (SD): control: 47.6 (12), lifestyle 48.9 (10.9). Gender (M:F): control: 8:2, lifestyle: 14/7. Ethnicity: Not stated

Study	Promrat 2010[786]
Further population details	
Extra comments	Baseline characteristics for control and lifestyle intervention groups respectively, mean (SD): ALT levels 85.5 (36.5), 85.6 (38.8); AST levels 66 (46.3), 57.5 (24.9); weight (kg/m2) 33.7 (4.7), 98.9 (23.9)
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Lifestyle modification - Any diet plus any exercise plus any behavioural therapy . Participants were seen in small groups (3-5 members) conducted by a Master's-level nutritionist or health educator, meeting weekly for the first 6 months and then biweekly for months 7 through 12. Diet: participants assigned a calorie goal based on their starting weight (1000–1200 kcal/day if baseline weight <200 lb or 1200–1500/day if baseline weight > 200 lb) and a daily fat gram goal designed to produce a 25% fat diet (28–33 g for 1000-kcal to 1200-kcal diet or 33–42 g for the 1200-kcal to 1500-kcal diet). Exercise: unsupervised exercise i.e. walking, participants given pedometers to encourage 10,000 steps per day, bicycling, aerobic dance, and strength training were also encouraged. Goal of 200 minutes per week of moderate-intensity physical activity by 6 months. Behaviour: participants self-monitored their eating and exercise daily, self-monitoring records reviewed weekly by the therapist in collaboration with the participant to identify areas of progress and areas in which further change would be advantageous. Stimulus control techniques, problem solving,27 and relapse prevention28 were taught in the weekly group sessions. Participants set individual behavioral goals and had discussions with the case manager. . Duration 12 months. Concurrent medication/care: Participants were allowed to start a new medication for management of hyperglycemia if medically necessary. Participants who were already taking thiazolidinediones or metformin had to be on a stable regimen for at least 6 months before study enrollment and initial liver biopsy. Exercise and reduced caloric consumption can produce hypoglycemia in patients with type 2 diabetes who are on insulin or sulfonylureas. Dose adjustment of these medications was conducted according to study protocol. (n=10) Intervention 2: No intervention / control - Control. Participants attended small group sessions providing basic education about NASH and about principles of healthy eating, physical activity, and weight control. These sessions occurred every 12 weeks and were conducted by a Master's-level nutritionist or health educator. Participants were not taught specific behavioral self-regulation skills to help them change behaviors. Duration 12 months. Concurrent medication/care: Participants were allowed to start a new medication for management of hyperglycemia if medically necessary. Participants who were already taking thiazolidinediones or metformin had to be on a stable regimen for at least 6 months before study enrollment and initial liver biopsy. Exercise and reduced caloric consumption can produce hypoglycemia in patients with type 2 diabetes who are on insulin or sulfonylureas. Dose adjustment of these medications was conducted according to study protocol.
Funding	Academic or government funding (National Institute of Health and the National Cancer Institute)

Study	Promrat 2010[786]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET PLUS ANY EXERCISE PLUS ANY BEHAVIOURAL THERAPY versus CONTROL Protocol outcome 1: NAFLD progression with liver biopsy at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): Fat at 48 weeks; Group 1: mean 1.9 (SD 0.9); n=18, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults (18 years and over): Parenchymal inflammation at 48 weeks; Group 1: mean 1.4 (SD 0.6); n=18, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults (18 years and over): Ballooning injury at 48 weeks; Group 1: mean 1.2 (SD 0.5); n=18, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults (18 years and over): Fibrosis at 48 weeks; Group 1: mean 4.4 (SD 1.1); n=18, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): NAS at 48 weeks; Group 2: mean 4.9 (SD 1); n=10; NAS 0-8 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with ultrasound at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; NAFLD progression with MRI / MRS at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; Liver function tests - ALT levels at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Weight (kg) at Greater or equal to 3 months; Liver function tests - AST levels at Greater or equal to 3 months

Study	Reinehr 2009[810]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in Germany; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ultrasound
Stratum	Young people (11 years or older and younger than 18 years)

Study	Reinehr 2009[810]
Subgroup analysis within study	Not applicable
Inclusion criteria	Obese children with NAFLD aged 6 to 16 years receiving regular school education
Exclusion criteria	Endocrine disorders, premature adrenarche, syndromal obesity, any regular medication, and families with parents or children declaring no motivation or couldn't find the time to attend regularly in the lifestyle intervention.
Age, gender and ethnicity	Age - Range: 6-16 years. Gender (M:F): Lifestyle intervention group 47% girls, control group 40% girls. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics - mean (SE): standard deviation score of BMI- treatment group 2.52 (0.04) control group 2.31 (0.08), ALT- treatment group 48 (2) control group 47 (2)
Indirectness of population	No indirectness
Interventions	(n=109) Intervention 1: Lifestyle modification - Any diet plus any exercise plus any behavioural therapy . Physical activity, nutrition advice (fat and sugar reduced diet with 15% protein, 55% carbohydrate, 30% fat and 5% sugar) and behavioural therapy including individual psychological care of the child and their family. Duration 1 year. Concurrent medication/care: Not stated (n=43) Intervention 2: No intervention / control - Control. 15 minute presentation as to a suitable diet, necessary physical exercise and behaviour patterns, they were given nutrition advice with written information and recipes.. Duration 1 year. Concurrent medication/care: Not stated
Funding	Academic or government funding (German federal ministry of education and research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET PLUS ANY EXERCISE PLUS ANY BEHAVIOURAL THERAPY versus CONTROL

Protocol outcome 1: NAFLD progression with ultrasound at Greater or equal to 3 months
- Actual outcome for Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined): NAFLD prevalence at 1 year; Group 1: 55/109, Group 2: 40/43; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests - AST levels at Greater or equal to 3 months
- Actual outcome for Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined): AST levels (U/L) at 1 year; Group 1: mean 29 (U/l) (SD 10.05); n=109, Group 2: mean 30 (U/l) (SD 6.56); n=43; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Liver function tests - ALT levels at Greater or equal to 3 months

Study	Reinehr 2009[810]
- Actual outcome for Young people (11 years or older and younger than 18 years) and children (younger than 11 years combined): ALT levels (U/L) at 1 year; Group 1: mean 38 U/l (SD 20.1); n=109, Group 2: mean 45 U/l (SD 32.79); n=43; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with liver biopsy at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; NAFLD progression with MRI / MRS at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Weight (kg) at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months

Study	Ueno 1997[983]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in Japan; Setting: Primary care for treatment group and home for control group
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fatty liver on ultrasound tomography
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with an obesity score of higher than 25 as determined by BMI and fatty liver on ultrasound tomographic findings such as bright liver or deep attenuation, and on histological diagnosis. Normal renal function, normal results of routine blood counts and no evidence of heart or lung disease.
Exclusion criteria	Patients with a history of excessive alcohol consumption (more than 80 grams/day for males and 40 grams/day for females, drug abuse, acute or chronic liver disease or transfusion, hep B surface antigen, antibody to hep B core antigen or antibody to hep C virus.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Treatment group 39 (13), control group 54 (10) years. Gender (M:F): 13/12. Ethnicity: Not stated
Further population details	

Study	Ueno 1997[983]
Extra comments	Baseline characteristics- mean (SD): weight (kg) TG 83 (13) CG 75 (7), AST (<40 IU) TG 66 (30) CG 64 (24), ALT (<35 IU) TG 83 (46) CG 73 (19)
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: No intervention / control - Control. Patients carried out their ordinary diet and lifestyle - aims of study described to patients. Duration 3 months. Concurrent medication/care: Not stated (n=15) Intervention 2: Diet and exercise - Any diet with any exercise. In-patient study: patients admitted into hospital for 1 month to undergo restricted diet and exercise therapy, they then followed the same therapy regimen at home for the subsequent 2 months. Diet: 25 Cal.kg-1 ideal body weight of conventional diet, with three meals/day provided (20% protein, 305 fat and 50% carbohydrate). Exercise: walking 3000 steps/day for 3 days, thereafter adding 500 steps every 3 days until 10,000 steps reached, then jogging for 20 minutes twice a day. . Duration 3 months. Concurrent medication/care: Not stated
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET WITH ANY EXERCISE versus CONTROL Protocol outcome 1: Liver function tests - AST levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): AST levels at 3 months; Group 1: mean 27 IU (SD 5); n=10, Group 2: mean 77 IU (SD 28); n=10; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests - ALT levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): ALT levels at 3 months; Group 1: mean 24 IU (SD 4); n=15, Group 2: mean 87 IU (SD 22); n=10; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with liver biopsy at Greater or equal to 3 months; NAFLD progression with ultrasound at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; NAFLD progression with MRI / MRS at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Weight (kg) at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months

Study	Wong 2013[1042]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=154)
Countries and setting	Conducted in China; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Screening with proton-magnetic resonance spectroscopy (1H-MRS)
Stratum	Adults (18 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-70 years, fatty liver 1H-MRS, defined as intrahepatic triglyceride (IHTG) content of 5% or above, and plasma alanine aminotransferase (ALT) above 30 U/l in men and 19 U/l in women.
Exclusion criteria	Subjects tested positive for hepatitis B surface antigen or anti-hepatitis C virus, or anti-nuclear antibody titre above 1/160, alcohol consumption above 20 grams a day in men and 10 grams a day in women, liver decompensation, and terminal illness and cancer including hepatocellular carcinoma.
Recruitment/selection of patients	Population screening for NAFLD in Hong Kong
Age, gender and ethnicity	Age: 18-70 years. Gender (M:F): Intervention group 41% male, control gorup 31% male. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics of intervention and control group respectively-mean (SD): Body weight (kg) 70.6 (11.9), 68.4 (9.8); BMI (kg/m2) 25.5 (3.9), 25.3 (3.2); ALT (U/l) 43 (28), 40 (23); AST (IU/U) 26 (12), 25 (12); IHTG (%) 12.3 (6.6), 12.2 (6.8); liver stiffness (kPa) 5.1 (1.8), 5.0 (1.7)
Indirectness of population	--
Interventions	(n=77) Intervention 1: Lifestyle modification - Any diet plus any exercise plus any behavioural therapy. Dietician-led lifestyle modification: attending diet consultation sessions weekly in the first 4 months, and monthly then on. First session the dietician carried out a complete behavioural assessment, follow up sessions included individualised menu plans with a varied diet emphasising fruit and vegetable, moderate carbohydrate, low-fat, low-glycaemic index and low calorific products in appropriate portions and increased proteins. Participants given a booklet on food portion size exchange and tips for eating out, and another listing low-GI food options and meal plans. Weekly food record kept to assess adherence. Patients also encouraged to see an exercise instructor who designed suitable exercise regimes for each patient: moderate intensity aerobic exercise for 30 minutes, 3/5 days a week. The intensity of the exercise was gradually increased to 30 minutes every day. Duration 1 year. Concurrent medication/care: All participants received

Study	Wong 2013[1042]
	individual education (n=77) Intervention 2: No intervention / control - Control. Usual care: patients encouraged to reduce carbohydrate and fat intake and exercise at least 3 times per week, 30 minutes per session. Duration 1 year. Concurrent medication/care: Not stated
Funding	Academic or government funding (National Research Foundation (United Kingdom), Chinese University of Hong Kong, Research Grants Council of the Hong Kong SAR)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY DIET PLUS ANY EXERCISE PLUS ANY BEHAVIOURAL THERAPY versus CONTROL Protocol outcome 1: NAFLD progression with ultrasound at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): Liver stiffness (kPa) at 1 year; Group 1: mean 4.6 (SD 1.4); n=77, Group 2: mean 5.2 (SD 1.9); n=77; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: NAFLD progression with MRI / MRS at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): IHTG (%) at 1 year; Group 1: mean 5.5 % (SD 5.9); n=77, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function tests - AST levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): AST level (U/l) at 1 year; Group 1: mean 22 (SD 8); n=77, Group 2: mean 22 (SD 8); n=77; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Liver function tests - ALT levels at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): ALT level (U/l) at 1 year; Group 1: mean 26 (SD 13); n=77, Group 2: mean 33 (SD 17); n=77; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Weight (kg) at Greater or equal to 3 months - Actual outcome for Adults (18 years and over): Body weight (kg) at 1 year; Group 1: mean 65 (SD 11); n=77, Group 2: mean 67.8 (SD 9.9); n=77; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with liver biopsy at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; NAFLD progression with NAFLD

Study	Wong 2013[1042]
	activity score (NAS) at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months

H.9 Alcohol advice

Reference	Ekstedt 2009[271]
Study type and analysis	Prospective longitudinal study. Patients had paired biopsies, or developed end stage liver failure, and fibrosis progression/regression was compared with alcohol intake using a multivariate analysis. Biopsies were analysed using the BRUNT scale.
Number of participants and characteristics	N= 104 (initial patients=137, 8 were classified as alcoholic liver disease (>140g/wk) and 25 died during follow-up) N included in study= 71 (16 patients refused follow up, 20 did not undergo further biopsy due to refusing (14), contraindicated (1) initial biopsy had cirrhosis) Inclusion criteria- asymptomatic patients , persistently elevated (>6 months) serum ALT and/or AST >41 U/L and /or elevated ALP >106 U/l Recruited: all referred patients to one gastroenterology department
Prognostic variable(s)	Alcohol consumption measured three variables: • a modified AUDIT C questionnaire with the addition of the question 'In what way has current (i.e. in the last 3 months) alcohol consumption changed compared with alcohol consumption before the first liver biopsy?', which were graded on a 5 point scale from decreased considerably to increased considerably. This was self-reported, and verified through an interview with a clinician, and any disparities were raised with the patient. • Weekly alcohol consumption at time of follow-up= the number of drinking occasions multiplied by the g of alcohol consumed on an average occasion • Heavy episodic drinking (HED=>60 g in males, and >48 g in females consumed in one occasion) was also measured. The variables extracted from these measures that were tested using the multivariate analysis included: • Alcohol consumption (g/week) • HED once a month or more often
Confounders OR stratification strategy	Patients were divided into fibrosis progression, regression and unchanged groups, an insignificant change defined as >1 fibrosis stage in the BRUNT scoring system, whilst a significant change included >2 stages, or end stage disease). There were two models used in the multivariate analysis as IR-HOMA could not be calculated in patients already receiving insulin, model 1= all patients (n-71) where IR-HOMA was not included as a confounder and Model 2 where patients not treated with insulin were included (n=57) were included where IR-HOMA was included.

Reference	Ekstedt 2009[271]
	Confounders included: • Age • Gender • BMI • Diabetes • Weight gain • IR HOMA (insulin resistance according to homeostasis model assessment) • Fibrosis stage at baseline • Alcohol consumption (g/week) • HED once a month or more often
Outcomes and effect sizes	Only significant variables were reported. Weekly alcohol consumption was not statistically significant; other variables measured including increase/decrease in alcohol during follow-up were not measured in the univariate/multivariate analysis. Heavy Episodic Drinking: OR= 42.148 (5.390-329.573), p value =<0.0001
Comments	Low risk of bias, assessor was blinded and there was a good alcohol history taken, although other variables measured including increase/decrease in alcohol during follow-up were not measured in the univariate/multivariate analysis. Alcohol limits defined similar to suggested UK intake.

Reference	Hashimoto 2015[404]
Study type and analysis	Retrospective longitudinal study. Participants had repeat liver ultrasounds (using a an ALoka SSD-650CL machine by technicians with the images reviewed by gastroenterologists blinded to baseline details) and these were compared with alcohol use using a multivariate analysis.
Number of participants and characteristics	n=5437 Inclusion criteria: All patients who had a health check-ups with ultrasound of the liver in 2003, and a repeat liver ultrasound in 2004-6 Exclusion criteria: Known liver disease or current use of any medication. Including those with positive serology for hepatitis B,antigen, or hepatitis C antibody and those who reported a history of known liver disease , including viral, genetic, autoimmune and drug induced liver disease. Setting: Japan, single centre, Recruited: Patients reporting for wellbeing checks, which were largely self-funded, or funded by companies/local government organisations.

	Fatty liver defined as: hepatorenal echo contrast and liver brightness
Prognostic variable(s)	Alcohol intake: self-reported validated questionnaire, asking the amount and type of alcoholic beverages consumed per week in the previous month. Divided into none or minimal intake <40g/week, light alcohol consumption 40-140g/week, moderate alcohol consumption 140-280 g/week and heavy >280g/week. Note that this follows japanese guidance on suggested alcohol intake, and there is no difference for men or women.
Confounders OR stratification strategy	Hazard risks of the grade of alcohol was calculated using the COX hazard model separately for men and women adjusting for: • Age • BMI • Smoker status • Regular exercise (defined as >1 episode of any type of sport undertaken per week)
Outcomes and effect sizes	At baseline: 807 men diagnosed with fatty liver, (75 of whom were heavy drinkers), at follow-up 81 had persistent fatty liver, and 726 had regressed. Of the 2640 women who did not have fatty liver at baseline, 857 developed fatty liver at follow up, and 1783 remained fatty liver free. 106 women diagnosed with fatty liver, (1 of whom was a heavy drinker), at follow-up 20 had persistent fatty liver, and 86 had regressed. Of the 1864 women who did not have fatty liver at baseline, 267 developed fatty liver at follow up, and 1617 remained fatty liver free. HR (95%CI, p value): Light Drinkers (40g-140g/week): Men 0.72 (0.60-0.86, <0.001), Women 0.86 (0.52-1.42, 0.56) Moderate drinkers (140g-280g/week): Men 0.69 (0.57-0.84, <0.001), Women 1.23 (0.62-2.41)]
Comments	High risk of bias. Patient's previous drinking history, or episodes of heavy drinking not assessed. No results presented for none or minimal alcohol provided. Indirect as the levels of alcohol not similar to UK values.

H.10 Caffeine advice

Study	**Catalano 2010** [175]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=245)
Countries and setting	Conducted in Italy; Setting: Primary care
Line of therapy	1st line

Study	Catalano 2010 [175]
Duration of study	Other: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ultrasound (bright liver score ≥1)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	NAFLD participants; ultrasound (bright liver score ≥1), referred by family doctor for evaluation and nutrition counselling at gastroenterology and nutrition unit. Controls; subjects referred to the same clinic without NAFLD.
Exclusion criteria	Severe chronic liver disease apart from lone finding of bright liver for NAFLD participants (controls no liver disease), congestive heart failure, renal failure oncological disease, thyroid disease, diabetes, alcohol history above 20 g/day in the last 5 years, previous HBV and/or HCV infections.
Recruitment/selection of patients	Referred by family doctor for evaluation and nutrition counselling at gastroenterology and nutrition unit
Age, gender and ethnicity	Age - Mean (SD): NAFLD participants 49.67 (13.52), controls (47.82 (10.39) years. Gender (M:F): 147/163. Ethnicity: Not reported
Further population details	
Extra comments	NAFLD participants versus control participants, mean (SD); BMI (kg/m2) 31.99 (5.52) versus 24.49 (3.57), AST (U/l) 24.13 versus 21.53 (7.08), ALT (U/l) 19.43 (6.28) versus 17.42 (5.45).
Indirectness of population	No indirectness
Interventions	(n=310) Intervention 1: Coffee - Caffeine. Coffee (cups/day). Duration 6 months. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAFFEINE FROM COFFEE [INTERVENTION 1] ONLY

Protocol outcome 1: NAFLD progression with ultrasound at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): Bright liver score at 6 months; Other: beta correlation coefficient -2.585 (95%CI -0.133 to -0.018); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests - ALT levels at Greater or equal to 3 months
- Actual outcome for Adults (18 years and over): ALT (U/l) at 6 months; Other: Correlation coefficient for cups of coffee = -0.091, p=0.259; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults (18 years and over): AST (U/l) at 6 months; Other: Correlation coefficient for coffee consumption; 0.128, p=0.326; Risk of bias: Very high;

Study	Catalano 2010 [175]
Indirectness of outcome: No indirectness Protocol outcome 3: Coffee (cups/day) at NA - Actual outcome for Adults (18 years and over): Coffee (cups/day) at 6 months; Other: NAFLD group; 2.25 (1.59) versus control group; 2.05 (1.71), p=0.282; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with liver biopsy at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; NAFLD progression with MRI / MRS at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Weight (kg) at Greater or equal to 3 months; Liver function tests - AST levels at Greater or equal to 3 months; Bland steatosis at NA; NASH stage 0 to 1 at NA; NASH stage 2 to 4 at NA; Fibrosis greater than or equal to 2 at NA; Negative ultrasound for NAFLD at NA

Study	Funatsu 2011 [333]
Study type	Other non-randomised study
Number of studies (number of participants)	1 (n=492)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Increase in alanine aminotransferase (ALT) levels for ≥6 months before the study, ultrasonography demonstrating fatty liver
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male office workers between age 25 and 60 years working at the same company.
Exclusion criteria	Treatment for chronic liver disease (chronic hepatitis, fatty liver, cirrhosis), hypertension, diabetes, incomplete patient records.
Recruitment/selection of patients	Office workers employed in the same service industry with no night shifts, recruited at annual physical health check-

Study	Funatsu 2011 [333]
	up
Age, gender and ethnicity	Age - Mean (SD): NAFLD group; 44.4 (7.6) years, control group; 44.2 (7.0) years. Gender (M:F): 492/0. Ethnicity: Asian
Further population details	
Extra comments	NAFLD group versus control group, mean (SD); BMI (kg/m2) 24.2 (2.3) versus 24.1 (2.0).
Indirectness of population	No indirectness
Interventions	(n=492) Intervention 1: Coffee - Caffeine. Cups/day. Duration 5 years. Concurrent medication/care: Annual lifestyle questionnaire mailed to participants for self-report prior to annual health check, included questions on all beverage consumption
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAFFEINE FROM COFFEE [INTERVENTION 1] ONLY Protocol outcome 1: NAFLD progression with ultrasound at Greater or equal to 3 months - Actual outcome: Ultrasound (increase in BLS, increase in liver kidney ratio and/or decrease in liver deep echo) at 5 years; OR 0.736 (95%CI 0.61 to 0.89); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Coffee (cups/day) at 5 years; Mean Coffee (cups/day), mean (SD); NAFLD group 2.3 (1.3) vs control group 3.0 (1.6), p<0.01; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	NAFLD progression with liver biopsy at Greater or equal to 3 months; Quality of life at Greater or equal to 3 months; NAFLD progression with fibroscan/ transient elastography at Greater or equal to 3 months; NAFLD progression with NAFLD fibrosis score at Greater or equal to 3 months; NAFLD progression with Enhanced Liver Fibrosis (ELF) score at Greater or equal to 3 months; NAFLD progression with MRI / MRS at Greater or equal to 3 months; Severe adverse event at Greater or equal to 3 months; NAFLD progression with NAFLD activity score (NAS) at Greater or equal to 3 months; Liver function tests - ALT levels at Greater or equal to 3 months; Liver function tests - ALT/AST ratio at Greater or equal to 3 months; Any adverse event at Greater or equal to 3 months; Weight (kg) at Greater or equal to 3 months; Liver function tests - AST levels at Greater or equal to 3 months; Bland steatosis at NA; NASH stage 0 to 1 at NA; NASH stage 2 to 4 at NA; Fibrosis greater than or equal to 2 at NA; Coffee (cups/day) at NA; Negative ultrasound for NAFLD at NA

H.11 Pharmacological interventions

Study	Aithal 2008[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in United Kingdom; Setting: Dual-centre study at two urban hospitals
Line of therapy	1st line
Duration of study	Other: 3-month run-in + 12 months intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Biopsy-proven NASH
Exclusion criteria	history of alcohol excess (weekly consumption of >210 g for men or >140 g for women), other liver diseases, drug treatment associated with fatty liver, diagnosed with diabetes mellitus before or at the time of recruitment, weight-reduction medication, pregnancy, lactating women, heart failure, renal impairment
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): Pioglitazone: 52 (28-71); placebo: 55 (27-73). Gender (M:F): Pioglitazone: 26/11; placebo: 19/18. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Insulin sensitisers - Pioglitazone. 30 mg/day. Duration 12 months. Concurrent medication/care: Reduction of calorie intake by 500 kcal/day, modest exercise (n=37) Intervention 2: Placebo. Not reported. Duration 12 months. Concurrent medication/care: Reduction of calorie intake by 500 kcal/day, modest exercise
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PIOGLITAZONE versus PLACEBO Protocol outcome 1: Progression of NAFLD at ≥12 months - Actual outcome for Adults: Decrease in steatosis score at 12 months; Group 1: 15/31, Group 2: 11/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Increase in steatosis score at 12 months; Group 1: 1/31, Group 2: 3/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Decrease in hepatocellular injury at 12 months; Group 1: 10/31, Group 2: 3/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Increase in hepatocellular injury at 12 months; Group 1: 4/31, Group 2: 12/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Decrease in lobular inflammation at 12 months; Group 1: 14/31, Group 2: 8/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Increase in lobular inflammation at 12 months; Group 1: 4/31, Group 2: 3/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Decrease in portal inflammation at 12 months; Group 1: 8/31, Group 2: 7/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Increase in portal inflammation at 12 months; Group 1: 8/31, Group 2: 11/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Decrease in Mallory-Denk bodies at 12 months; Group 1: 8/31, Group 2: 1/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Increase in Mallory-Denk bodies at 12 months; Group 1: 0/31, Group 2: 3/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Decrease in fibrosis at 12 months; Group 1: 9/31, Group 2: 6/30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Increase in fibrosis at 12 months; Group 1: 0/31, Group 2: 6/30; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests at ≥12 months - Actual outcome for Adults: Mean ALT level at 12 months; Group 1: mean 55.9 U/L (SD 25.7); n=37, Group 2: mean 77.2 U/L (SD 43); n=37; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥3 to <12 months

Study	**Akcam 2011[24]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=67)
Countries and setting	Conducted in Turkey; Setting: Outpatient clinic of a Department of Paediatric Endocrinology and a university hospital in Turkey.
Line of therapy	1st line
Duration of study	Intervention time: 6 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: NAFLD diagnosis using ultrasonography scored according to the hyperechogenicity of the liver tissue, discrepancy between liver and diaphragm, and visibility of vascular structures.
Stratum	Young people and children: Obese adolescents (9-17 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	9-17 years of age, with BMI ≥ the 95th percentile for age and gender based on the US Centres for Disease Control and Prevention, and with liver steatosis.
Exclusion criteria	Diagnosed disease including type 1 or type 2 diabetes mellitus, took medications, or had a condition known to influence body composition, insulin action, or insulin secretion (e.g. glucocorticoid therapy, hypothyroidism, Cushing's disease).
Recruitment/selection of patients	Obese adolescents with liver steatosis who attended the the clinic and whose parents gave consent.
Age, gender and ethnicity	Age - Mean (SD): Metformin group 12 (2.9); Vit E group 12.6 (2.3); no treatment group (not analysed in this review) 12.3 (2.6). Gender (M:F): Metformin group 11/11; Vit E group 11/12; no treatment group (not analysed in this review) 10/12.. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear (Excluded from this review.).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Insulin sensitisers - Metformin. Oral treatment with 850mg daily (Glucophage, Bristol-Myers Squibb). Medication taken with meals to minimise gastrointestinal side-effects.. Duration 6 months. Concurrent medication/care: Patients in all groups were advised to adopt a diet supplying 30 kcal/kg based on current body weight; 50% of the diets energy was derived from carbohydrates, 30% from lipids, and 20% from proteins. All patients received a list of recommended food portions and possible combinations. All patients were advised to perform at least 30 mins of aerobic physical activity per day. Both groups had diet and exercise advice individually tailored to each patient. Each patient attended individual consultation sessions with a registered paediatric nutritionist, who checked the list of recommended and restricted food and amounts, and compliance with these recommendations. (n=23) Intervention 2: Vitamin E. Oral capsules 400 U/daily self-administered. Duration 6 months. Concurrent medication/care: Patients in all groups were advised to adopt a diet supplying 30 kcal/kg based on current body weight; 50% of the diets energy was derived from carbohydrates, 30% from lipids, and 20% from proteins. All patients received a list of recommended food portions and possible combinations. All patients were advised to perform at least 30 mins of aerobic physical activity per day. Both groups had diet and exercise advice individually tailored to each patient. Each patient attended individual consultation sessions with a registered paediatric nutritionist, who checked the list of recommended and restricted food and amounts, and compliance with these recommendations.
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN versus VITAMIN E Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months - Actual outcome for Young people and children: Improvements in steatosis detected by ultrasound at 6 months; Group 1: 15/22, Group 2: 8/23; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events at ≥3 to <12 months - Actual outcome for Young people and children: Minor side effects at 6 months; Group 1: 2/22, Group 2: 0/23; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function tests at ≥3 to <12 months - Actual outcome for Young people and children: Change in triglycerides (mg/dL) at 6 months; Group 1: mean 25.5 mg/dL (SD 44.8); n=22, Group 2: mean 14.5 mg/dL (SD 49.9); n=23; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcomes not reported by the study	Quality of life at ≥12 months; Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	**Belfort 2006[118]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=55 (no information given on number randomised to each group))
Countries and setting	Conducted in USA; Setting: secondary care, dual-centre study
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	NASH with impaired OGTT or type-II diabetes
Exclusion criteria	Normal results on the OGTT, abnormal findings on laboratory tests, AST or ALT levels 2.5 times or more the upper limit

	of the normal range, history of heavy alcohol use (>12 to 15g of alcohol per day, or >12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits), fasting glucose level of 240mg per decilitre (13.3mmol per litre) or greater, type-I diabetes, heart disease, hepatic disease (other than NASH), renal disease, drug treatment (metformin, thiazolidinediones, insulin)
Recruitment/selection of patients	unclear
Age, gender and ethnicity	Age - Mean (SD): Placebo: 51 (±10); Pioglitazone: 51 (±7). Gender (M:F): Placebo: 7/14; Pioglitazone: 14/12. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Type 2 diabetes
Extra comments	Placebo: AST 42 (±16), ALT 61 (±33); Pioglitazone: AST 47 (±15), ALT 67 (±26)
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Insulin sensitisers - Pioglitazone. 30mg/d (increased to 45mg/d after 2 months), Actos. Duration 6 months. Concurrent medication/care: Patients were asked to reduce their caloric intake by 500 kcal/d pror to randomisation. (n=21) Intervention 2: Placebo. Placebo. Duration 6 months. Concurrent medication/care: Patients were asked to reduce their caloric intake by 500 kcal per day prior to randomisation.
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PIOGLITAZONE versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months
- Actual outcome for Adults: Number of patients with improvement in steatosis at 6 months; Group 1: 17/26, Group 2: 8/21; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Number of patients with improvement in ballooning necrosis at 6 months; Group 1: 14/26, Group 2: 5/21; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Number of patients with improvement in lobular inflammation at 6 months; Group 1: 17/26, Group 2: 6/21; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Number of patients with improvement in fibrosis at 6 months; Group 1: 12/26, Group 2: 7/21; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Number of patients with a reduction in steatosis score of ≥2 at 6 months; Group 1: 9/21, Group 2: 0/14; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Number of patients with a reduction in fibrosis score of ≥2 at 6 months; Group 1: 12/5, Group 2: 6/1; Risk of bias: Very high; Indirectness of

outcome: No indirectness Protocol outcome 2: Liver function tests at ≥3 to <12 months - Actual outcome for Adults: Mean ALT levels at 6 months; Group 1: mean 28 U/L (SD 12); n=26, Group 2: mean 40 U/L (SD 17); n=21; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean AST levels at 6 months; Group 1: mean 28 U/L (SD 7); n=26, Group 2: mean 33 U/L (SD 10); n=21; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	**Bugianesi 2005[151]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Italy; Setting: Double-centre study at two university hospitals
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	alcohol consumption > 20 g/day, positive screening for hepatitis B or C, autoimmune phenomena indicating autoimmune hepatitis or celiac disease, presence of gene markers of familial hemochromatosis, previously diagnosed diabetes due to treatment with metformin, BMI ≥ 35 kg/m2
Recruitment/selection of patients	Recruited among patients referred to the hospital for elevated ALT levels, exceeding 1.5 times normal values for 6 months or more
Age, gender and ethnicity	Age - Mean (SD): Bologna unit: metformin: 42 (±10), vitamin E: 40 (±10); Turin unit: metformin: 45 (±10). Gender (M:F): Bologna Unit: 22/7 (metformin), 28/0 (vitamin E); Turin Unit: 18/8 (metformin). Ethnicity: Not reported

Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	--
Interventions	(n=28) Intervention 1: Vitamin E. 400 IU twice per day (daily dose of 800 IU). Duration 12 months. Concurrent medication/care: Patients were advised to walk or jog at least 30 mins per day (n=29) Intervention 2: Insulin sensitisers - Metformin. 2000 mg/d, dosage was progressively increased from 250 mg/d twice to reduce gastrointestinal side effects. Duration 12 months. Concurrent medication/care: Patients were advised to walk or jog at least 30 mins per day Comments: Accounts for the Bologna arm (n=29) only
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN versus VITAMIN E Protocol outcome 1: Liver function tests at ≥12 months - Actual outcome for Adults: Number of patients with normalised ALT levels at 12 months; Group 1: 13/29, Group 2: 4/28; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥3 to <12 months

Study (subsidiary papers)	**Dufour 2006[260] (Balmer 2009[107])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in Switzerland
Line of therapy	Unclear
Duration of study	Intervention time: 2 years

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Elevated serum ALT levels of at least 1.5 times the upper limit of normal for at least 6 months
Stratum	Adults
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Patients aged 18 to 75 years old with elevated serum ALT levels of at least 1.5 times the upper limit of normal for at least 6 months and a weekly alcohol consumption of less than 40 grams, had a liver biopsy performed no more than 6 months before inclusion showing macrovesicular steatosis of more than 10% of the hepatocytes, hepatocellular injury (ballooning, dropout) and lobular inflammation.
Exclusion criteria	Laboratory (serologies for hepatitis B and hepatitis C virus, abnormal transferrin saturation, low a1-antitrypsin, antinuclear antibodies superior to 1:80, antimitochondrial antibodies) or histologic findings suggestive of another liver disease, decompensated cirrhosis, serious disease limiting life expectancy, pregnant or lactating women, treatment with a drug known to induce NASH and oral anti-coagulation.
Age, gender and ethnicity	Age - Mean (SD): UDCA+VitE 47 (14), UDCA 47 (12), placebo 46 (13). Gender (M:F): UDCA+VitE 64% male, UDCA 57% male, placebo 54% male. Ethnicity: Not stated
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Extra comments	Baseline characteristics, mean (SD): UDCA+VitE 2.6 (1.2) male, UDCA 3 (0.9), placebo 2.9 (0.7)
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Combination of 2 pharmacological interventions. Ursodeoxycholic acid (UDCA) (250 mg) and vitamin E (400 IU), UDCA 12-15 mg/kg/day and 400 IU vitamin twice a day . Duration 2 years. Concurrent medication/care: Patients informed of the benefits of regularly exercising and if over weight, of weight loss. (n=14) Intervention 2: Ursodeoxycholic acid. UDCA 250 mg 12-15 mg/kg/day. Duration 2 years. Concurrent medication/care: Patients informed of the benefits of regularly exercising and if over weight, of weight loss. (n=13) Intervention 3: Placebo. Placebo tablets. Duration 2 years. Concurrent medication/care: Patients informed of the benefits of regularly exercising and if over weight, of weight loss.
Funding	Equipment / drugs provided by industry (Falk Pharma provided support to buy ELISA kits and author supported by the Stifung fur die Leberkranheiten)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION OF 2 PHARMACOLOGICAL INTERVENTIONS versus URSODEOXYCHOLIC ACID

Protocol outcome 1: Progression of NAFLD at ≥12 months - Actual outcome for Adults: Steatosis at 2 years; Group 1: mean 1.4 (SD 1.5); n=14, Group 2: mean 2.6 (SD 1.1); n=14; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Change in steatosis, hepatocellular injury and parenchymal inflammation at 2 years; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION OF 2 PHARMACOLOGICAL INTERVENTIONS versus PLACEBO Protocol outcome 1: Progression of NAFLD at ≥12 months - Actual outcome for Adults: Steatosis at 2 years; Group 1: mean 1.4 (SD 1.5); n=14, Group 2: mean 2.5 (SD 1.3); n=13; Steatosis 0-4 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Change in steatosis, hepatocellular injury and parenchymal inflammation at 2 years; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: URSODEOXYCHOLIC ACID versus PLACEBO Protocol outcome 1: Progression of NAFLD at ≥12 months - Actual outcome for Adults: Steatosis at 2 years; Group 1: mean 2.6 (SD 1.1); n=14, Group 2: mean 2.5 (SD 1.3); n=13; Steatosis 0-4 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Change in steatosis, hepatocellular injury and parenchymal inflammation at 2 years; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months; Liver function tests at ≥3 to <12 months

Study	**Harrison 2009[395]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in USA; Setting: Dual-centre study at two urban medical centres

Line of therapy	1st line
Duration of study	Intervention time: 36 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	25 patients were enrolled from each site
Age, gender and ethnicity	Age - Mean (SD): 47.0 (±9). Gender (M:F): Define. Ethnicity: 68.3% Caucasian, 26.8% Hispanic, 4.8% African American or Asian
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Vitamin E. 800 IU vitamin E per day. Duration 36 weeks. Concurrent medication/care: a single multivitamin tablet at bedtime, 1400-calorie/day diet (n=25) Intervention 2: Combination of 2 pharmacological interventions. 120 mg orlistat orally three times a day with meals + 800 IU vitamin E per day. Duration 36 weeks. Concurrent medication/care: a single multivitamin tablet at bedtime, 1400-calorie/day diet
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION OF 2 PHARMACOLOGICAL INTERVENTIONS versus VITAMIN E

Protocol outcome 1: Liver function tests at ≥3 to <12 months
- Actual outcome for Adults: Mean ALT levels at 36 weeks; Group 1: mean 53 U/L (SD 41); n=23, Group 2: mean 38 U/L (SD 26); n=18; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean AST levels at 36 weeks; Group 1: mean 36 U/L (SD 17); n=23, Group 2: mean 32 U/L (SD 21); n=18; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12

	months; Progression of NAFLD at ≥12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	**Haukeland 2009[409]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Norway; Setting: Four university hospitals
Line of therapy	1st line
Duration of study	Intervention time: 1/4 centres 31 months, 3/4 centres 12-18months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Liver biopsy-proven NAFLD
Stratum	Adults: Adults with histologically verified NAFLD within 18 months prior to inclusion
Subgroup analysis within study	Not applicable: None conducted.
Inclusion criteria	Biopsy-proven NAFLD. Additional inclusion criteria required for patients with simple steatosis, in whom elevated transaminases (>ULN) and impaired glucose tolerance or T2D would be present.
Exclusion criteria	Weight change of more than 5kg since the time of biopsy, previous or ongoing treatment with insulin, metformin or thiazolidinediones, kidney failure, pharmacologically treated heart failure, significant coronary heart disease, moderate to severe chronic obstructive lung disease, liver cirrhosis or liver diseases other than NAFLD and alcohol consumption > 24 g/day
Recruitment/selection of patients	In one hospital inclusion occurred from November 2004 to July 2007. In the remaining hospitals recruitment was limited to shorter periods (12-18 months).
Age, gender and ethnicity	Age - Mean (SD): Metformin group 44.3 (9.0); placebo group 49.9 (12.8). Gender (M:F): 32/12. Ethnicity: Caucasian 86%
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear (Abnormal glucose tolerance: metformin group 45% v. placebo group 50%; Type 2 diabetes mellitus: metformin group 20% v. placebo group 33%; Hypertension: metformin group 25% v. placebo group 54%. No stratification or subgrouping of results.).
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Insulin sensitisers - Metformin. Treatment started with one tablet a day (500 mg) and study medication increased every week until a maximal daily dose of 2500 mg or 3000 mg (if bodyweight >90 kg) was reached

	after 4 or 5 weeks. If side-effects occured the dose was reduced temporarily or permanently to a level that was tolerated by the person.. Duration 6 months. Concurrent medication/care: At enrolment all participants received general advice about healthy lifestyle, i.e. physical activity at least 30 mins daily and a diet low in fat, particularly saturated fat, and refined carbohydrates. (n=24) Intervention 2: Placebo. Treatment started with one tablet a day (placebo) and study medication increased every week until a maximal daily dose of 2500 mg or 3000 mg (if bodyweight >90 kg) was reached after 4 or 5 weeks. If side-effects occurred the dose was reduced temporarily or permanently to a level that was tolerated by the person. Unclear what placebo tablet contained.. Duration 6 months. Concurrent medication/care: At enrolment all participants received general advice about healthy lifestyle, i.e. physical activity at least 30 mins daily and a diet low in fat, particularly saturated fat, and refined carbohydrates.
Funding	Equipment / drugs provided by industry (Work supported by Eastern Norway Regional Health Authority (grant) and Merck Sante (delivery of study medication).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months
- Actual outcome for Adults: Proportion with improvement in steatosis (as a categorical variable <5%, 5-33%, >33-66%, >66%) at 6 months; Group 1: 5/20, Group 2: 9/24; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Proportion with improvement in ballooning necrosis score (as a categorical variable 0-none, 1-few ballooned cells, 2-many ballooned cells) at 6 months; Group 1: 1/20, Group 2: 3/24; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Proportion with improvement in lobular inflammation score (as a categorical variable 0: none foci, 1: 0-1 foci per 200 x field, 2: 2-4 foci per 200 x field, 3: >4 foci per 200 x field) at 6 months; Group 1: 3/20, Group 2: 8/24; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Proportion with improvement in fibrosis score (as a categorical variable 0: none, 1: perisinusoidal or periportal, 2: perisinusoidal and periportal, 3: bridging fibrosis, 4: cirrhosis) at 6 months; Group 1: 1/20, Group 2: 4/24; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Proportion with improvement in NAFLD activity score (NAS) at 6 months; Group 1: 4/20, Group 2: 12/24; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥3 to <12 months
- Actual outcome for Adults: Median reduction of serum ALT at 6 months; Other: metformin 22 U/l v. placebo 15 U/l; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Median reduction of serum AST at 6 months; Other: metformin 8 U/l vs. no median reduction in placebo group; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥12 months; Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	**Lee 2008[580]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Singapore; Setting: Single-centre study at a gastroenterology clinic
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	persistently abnormal ALT (>1.5 times the upper normal limit and repeated at least twice over 6 months), US or CAT scan showing fatty infiltration, histologic evidence of NASH
Exclusion criteria	other causes of liver disease, decompensated liver disease (bilirubin ≥35 micromol/l, serum albumin of >35 g/l, or an INR ≥1.7), overt ascites and/or gastrointestinal bleeding documented on upper GI endoscopy, ongoing total parenteral nutrition, jejunal-ileal bypass, HIV infection, alcohol intake of more than 30g a week in the past 6 months or a history of alcohol dependence, pregnancy or lactation, hypersensitivity to methylxanthines, concomitant use of ketorolac, recent retinal/cerebral haemorrhage, acute myocardial infarction or severe cardiac arrhythmias and impaired renal function
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): PTX: 47.00 (±8.39) versus 47.89 (±14.05). Gender (M:F): PTX: 7/4; placebo: 6/3. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Pentoxifylline. 400 mg three times a day. Duration 12 weeks. Concurrent medication/care: low-calorie diet (1500 kcal/day for men, 1200 kcal/day for women), daily exercise (n=9) Intervention 2: Placebo. Three times a day. Duration 12 weeks. Concurrent medication/care: low-calorie diet

	(1500 kcal/day for men, 1200 kcal/day for women), daily exercise
Funding	Academic or government funding (National Healthcare Group Small Innovative Grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PENTOXIFYLLINE versus PLACEBO Protocol outcome 1: Liver function tests at ≥3 to <12 months - Actual outcome for Adults: Mean ALT level at 12 weeks; Group 1: mean 50.73 U/L (SD 15.71); n=11, Group 2: mean 75.44 U/L (SD 34.7); n=9; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean AST level at 12 weeks; Group 1: mean 33.18 U/L (SD 6.87); n=11, Group 2: mean 49.33 U/L (SD 19.2); n=9; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	**Leuschner 2010[583]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=186)
Countries and setting	Conducted in Germany, Greece; Setting: Multi-centre study with 25 participating centres in 2 countries
Line of therapy	Unclear
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Progression of NAFLD (NAS), liver function tests (ALT, AST)
Stratum	Adults
Subgroup analysis within study	Not stratified but pre-specified: age (<50 years and ≥50 years), inflammation (sum score >7 points), improvement of ALT (by ≥50%), BMI (≤30 kg/m2 and >30 kg/m2), blood pressure (<130/85 mm Hg and ≥130/85 mm Hg)
Inclusion criteria	Written informed consent, patients of both sexes (≥18 years old), diagnosis of NASH with three of the following criteria proven by biopsy (steatosis, ballooning, lobular inflammation, fibrosis, Mallory-Denk bodies), ALT level at least 1.5 times

	the upper limit of normal, 3 criteria of the metabolic syndrome, type-2 diabetes or hypertriglyceridemia or BMI > 25 kg/m2, alcohol consumption < 70 g/week
Exclusion criteria	liver cirrhosis, hepatitis B or C markers, antinuclear antibody/smooth muscle antibody titers >1:160, cholestatic liver disease, Wilson's disease, alpha-1 antitrypsin deficiency, hemochromatosis, history of HIV, recent intake of potential liver-toxic drugs or drugs interacting with UDCA, treatment with drugs (UDCA, glitazones, metformin, vitamin E, angiotensin II receptor antagonists) in the last 3 months prior to study entry, alcohol consumption > 70 g/week, mean corpuscular volume >101 fL, pregnancy, lactation, insufficient contraception in fertile women, patients considered to be unreliable or not compliant
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): UDCA: 41.45 (18-71); placebo: 45.02 (18-73). Gender (M:F): 63/32 (UDCA), 63/28 (placebo group). Ethnicity: 94% Caucasian (UDCA group), 99% Caucasian (placebo group)
Further population details	1. Extra-hepatic condition: Hypertension
Indirectness of population	No indirectness
Interventions	(n=95) Intervention 1: Ursodeoxycholic acid. 23-28 mg/kg of body weight/day; administered in three divided doses daily. Duration 18 months. Concurrent medication/care: Not reported (n=91) Intervention 2: Placebo. Administered in three divided doses daily. Duration 18 months. Concurrent medication/care: Not reported
Funding	Study funded by industry (Supported by Dr Falk Pharma GmbH)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: URSODEOXYCHOLIC ACID versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥12 months
- Actual outcome for Adults: Change in NAS (overall histology) at 18 months; Group 1: mean -1.22 (SD 1.21); n=69, Group 2: mean -1.03 (SD 1.38); n=68; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Change is steatosis at 18 months; Group 1: mean -0.52 (SD 0.65); n=69, Group 2: mean -0.48 (SD 0.69); n=68; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Change is ballooning at 18 months; Group 1: mean -0.12 (SD 0.53); n=69, Group 2: mean -0.21 (SD 0.55); n=68; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Change is lobular inflammation at 18 months; Group 1: mean -0.38 (SD 0.62); n=69, Group 2: mean -0.15 (SD 0.56); n=68; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Adults: Change is fibrosis at 18 months; Group 1: mean 0 (SD 0.55); n=69, Group 2: mean 0.08 (SD 0.43); n=68; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests at ≥12 months - Actual outcome for Adults: Change in mean ALT levels at 18 months; Group 1: mean -40.63 U/L (SD 58.37); n=95, Group 2: mean -38.15 U/L (SD 62.6); n=91; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults: Change in mean AST levels at 18 months; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥3 to <12 months

Study	**Lindor 2004**[588]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=174)
Countries and setting	Conducted in Canada, USA; Setting: Multi-centre study with 13 participating centres in two countries
Line of therapy	Unclear
Duration of study	Intervention time: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	persistent elevation of ALT or AST at least 1.5 times the upper limits of normal for at least 3 months, weekly alcohol consumption of less than 40 g, liver biopsy within the previous 6 months showing greater than 10% steatosis along with lobular necroinflammatory changes
Exclusion criteria	treatment with UDCA or chenodeoxycholic acid in the 3 months prior to study, anticipated need for transplantation within 1 year or recurrent variceal bleeding, spontaneous portosystemic encephalopathy, diuretic-resistant ascites, bacterial peritonitis, pregnancy or lactation, treatment with any drugs associated with steatohepatitis in 6 months prior to study, laboratory or histologic findings highly suggestive of liver disease of another aetiology, less than 18 years old or older than 75 years

Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): UCDA: 45.4 (±12.0); placebo: 48.5 (±11.6). Gender (M:F): 36/44 (UCDA), 37/49 (placebo). Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Ursodeoxycholic acid. 13-15 mg/kg body weight/day; administered orally in 4 divided doses. Duration 24 months. Concurrent medication/care: Not reported (n=86) Intervention 2: Placebo. Administered orally in 4 divided doses per day. Duration 24 months. Concurrent medication/care: Not reported
Funding	Study funded by industry (Partially supported by Axcan Pharma Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: URSODEOXYCHOLIC ACID versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥12 months
- Actual outcome for Adults: Mean overall steatosis difference at 24 months; Group 1: mean -0.4 (SD 0.6); n=50, Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean overall fibrosis difference at 24 months; Group 1: mean 0 (SD 0.1); n=50, Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥12 months
- Actual outcome for Adults: Mean ALT difference at 24 months; Group 1: mean -32.7 U/L (SD 69.8); n=56, Group 2: mean -31.6 U/L (SD 67.3); n=61; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean AST difference at 24 months; Group 1: mean -21.7 U/L (SD 53.2); n=55, Group 2: mean -20.7 U/L (SD 43.8); n=64; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥3 to <12 months

Study	Nelson 2009[694]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in USA; Setting: Single-centre study at an army medical centre
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	compensated liver disease with haemoglobin values of ≥12 g/dL (women) or ≥13 g/dL (men), white blood cell count of > 3000/mm3, neutrophil count >1500/mm3, platelets >70,000/m3, albumin >3.0 g/dL, normal total bilirubin, normal prothrombin time, normal INR, serum creatinine <1.4 mg/dL, elevated serum lipid panel (either total cholesterol >200 mg/dL, LDL >130 mg/dL or TGs >200 mg/dL)
Exclusion criteria	other causes of chronic liver disease, history of alcohol consumption >1 drink per day, prior surgical disease (including gastroplasty, jejuno-ileal or jejuno-colic bypass), prior exposure to organic solvents (such as carbon tetrachloride), total parenteral nutrition within the previous 6 months, prior organ transplantation, prior treatment with a statin within the past 12 weeks, use of certain medication (tamoxifen, prednisone, chloroquine, methotrexate, highly active retroviral therapy, amiodarone, other hepatotoxic medication), serum transaminases >3 times the upper limit of normal
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Statin group: 52.6 (±8.6); placebo group: 52.5 (±13.0). Gender (M:F): Statin group: 7/3; placebo group: 4/2. Ethnicity: 11 White, 3 Hispanic, 2 African American
Further population details	1. Extra-hepatic condition: dyslipidaemia
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Statins. 40 mg simvastatin once per day. Duration 12 months. Concurrent medication/care: Not reported (n=6) Intervention 2: Placebo. Once per day. Duration 12 months. Concurrent medication/care: Not reported
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STATINS versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥12 months
- Actual outcome for Adults: Mean fibrosis stage at 12 months; Group 1: mean 1.5 (SD 0.9); n=10, Group 2: mean 1 (SD 1.4); n=6; NAFLD fibrosis score 0-4 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Percentage of steatosis at 12 months; Group 1: mean 23.8 % (SD 21.2); n=10, Group 2: mean 20 % (SD 21.2); n=6; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Necroinflammatory activity at 12 months; Group 1: mean 1.4 (SD 0.5); n=10, Group 2: mean 1 (SD 1.4); n=6; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥12 months
- Actual outcome for Adults: Mean ALT levels at 12 months; Group 1: mean 49.5 U/L (SD 15.6); n=10, Group 2: mean 75.3 U/L (SD 25.9); n=6; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean AST levels at 12 months; Group 1: mean 36.5 U/L (SD 11.5); n=10, Group 2: mean 49.3 U/L (SD 9.5); n=6; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥3 to <12 months

Study (subsidiary papers)	**PIVENS trial: Sanyal 2010[833] (Bell 2012[119])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=247)
Countries and setting	Conducted in USA
Line of therapy	Unclear
Duration of study	96 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: liver biopsy: absent, possible or definite steatohepatitis
Stratum	Adults

Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Adults without diabetes who had NASH, diagnosed by the liver biopsy as possible or definite, and NAFLD activity score of 5 or more, definite steatohepitis with activity scorfe of 4, a score of atleast 1 for hepatocellular ballooning in each participant.
Exclusion criteria	Alcohol consumption of more than 20 grams per day for women and 30 grams for men, cirrhosis, hepatitis C, other liver diseases, heart failure, or if they were receiving drugs known to cause statohepatitis.
Age, gender and ethnicity	Age - Mean (SD): 46.3 (11.9). Gender (M:F): 40/60%. Ethnicity: Not stated
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Extra comments	Baseline characteristics of placebo, vitamin E amd pioglitazone groups respectively, mean (SD: ALT 81 (48), 86 (52), 82 (45); AST 55 (30), 59 (33), 54 (26); NAFLD activity score 4.8 (1.4), 5.1 (1.4), 5.0 (1.4)
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Insulin sensitisers - Pioglitazone. Piaglitazone at 30 mg once per day, with a vitamin E like placebo. Duration 96 weeks. Concurrent medication/care: Not stated (n=84) Intervention 2: Vitamin E. Vitamin E at 800 IU a day with pioglitazone like placebo. Duration 96 weeks. Concurrent medication/care: Not stated (n=83) Intervention 3: Placebo. Pioglitazone like placebo and vitamin E like placebo once a day. Duration 96 weeks. Concurrent medication/care: Not stated
Funding	Other (National institute of health, NIH general clinical research grants, clinical and translational science awards, Takeda Pharmaceuticals North America, Vitamin E softgels and matching placebo provided by Pharmavite.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PIOGLITAZONE versus VITAMIN E

Protocol outcome 1: Quality of life at ≥12 months
- Actual outcome for Adults: SF-36 score (physical component) at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: SF-36 score (mental component) at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality at ≥12 months
- Actual outcome for Adults: Mortality at 96 weeks; Group 1: 0/80, Group 2: 1/84; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Progression of NAFLD at ≥12 months
- Actual outcome for Adults: Total NAFLD activity score at 96 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Steatosis-subjects with improvement at 96 weeks; Group 1: 55/80, Group 2: 45/84; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Fibrosis-subjects with improvement at 96 weeks; Group 1: 35/80, Group 2: 34/84; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Subjects with improvement at 96 weeks; Group 1: 27/80, Group 2: 36/84; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Lobular inflammation-subjects with improvement at 96 weeks; Group 1: 48/80, Group 2: 45/84; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Hepatocellular ballooning-subjects with improvement at 96 weeks; Group 1: 35/80, Group 2: 42/84; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Hepatocellular ballooning-subjects with improvement at 96 weeks; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Resolution of NASH at 96 weeks; Group 1: 38/80, Group 2: 30/84; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Serious adverse events at ≥12 months
- Actual outcome for Adults: Severe adverse e vents at 96 weeks; Group 1: 2/80, Group 2: 7/84; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse events at ≥12 months
- Actual outcome for Adults: Cardiovascular adverse e vents at 96 weeks; Group 1: 10/80, Group 2: 12/84; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: Liver function tests at ≥12 months
- Actual outcome for Adults: ALT levels at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: AST levels at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PIOGLITAZONE versus PLACEBO

Protocol outcome 1: Quality of life at ≥12 months
- Actual outcome for Adults: SF-36 score (physical component) at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: SF-36 score (mental component) at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of NAFLD at ≥12 months
- Actual outcome for Adults: Total NAFLD activity score at 96 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Steatosis-subjects with improvement at 96 weeks; Group 1: 55/80, Group 2: 26/83; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Fibrosis-subjects with improvement at 96 weeks; Group 1: 35/80, Group 2: 26/83; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Adults: Subjects with improvement at 96 weeks; Group 1: 27/80, Group 2: 16/83; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Lobular inflammation-subjects with improvement at 96 weeks; Group 1: 48/80, Group 2: 29/83; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Hepatocellular ballooning-subjects with improvement at 96 weeks; Group 1: 35/80, Group 2: 24/83; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Hepatocellular ballooning-subjects with improvement at 96 weeks; Group 1: 35/80, Group 2: 24/83; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Resolution of NASH at 96 weeks; Group 1: 38/80, Group 2: 17/83; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse events at ≥12 months
- Actual outcome for Adults: Severe adverse e vents at 96 weeks; Group 1: 2/80, Group 2: 10/83; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse events at ≥12 months
- Actual outcome for Adults: Cardiovascular adverse e vents at 96 weeks; Group 1: 10/80, Group 2: 12/83; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 5: Liver function tests at ≥12 months
- Actual outcome for Adults: ALT levels at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: AST levels at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VITAMIN E versus PLACEBO

Protocol outcome 1: Quality of life at ≥12 months
- Actual outcome for Adults: SF-36 score (physical component) at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: SF-36 score (mental component) at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality at ≥12 months
- Actual outcome for Adults: Mortality at 96 weeks; Group 1: 1/84, Group 2: 0/83; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Progression of NAFLD at ≥12 months
- Actual outcome for Adults: Total NAFLD activity score at 96 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Steatosis-subjects with improvement at 96 weeks; Group 1: 45/84, Group 2: 26/83; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Fibrosis-subjects with improvement at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Subjects with improvement at 96 weeks; Group 1: 36/84, Group 2: 16/83; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Lobular inflammation-subjects with improvement at 96 weeks; Group 1: 45/84, Group 2: 29/83; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Adults: Hepatocellular ballooning-subjects with improvement at 96 weeks; Group 1: 42/84, Group 2: 24/83; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Hepatocellular ballooning-subjects with improvement at 96 weeks; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome for Adults: Resolution of NASH at 96 weeks; Group 1: 30/84, Group 2: 17/83; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events at ≥12 months - Actual outcome for Adults: Severe adverse e vents at 96 weeks; Group 1: 7/84, Group 2: 10/83; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse events at ≥12 months - Actual outcome for Adults: Cardiovascular adverse e vents at 96 weeks; Group 1: 12/84, Group 2: 12/83; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Liver function tests at ≥12 months - Actual outcome for Adults: ALT levels at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: AST levels at 96 weeks; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Liver function tests at ≥3 to <12 months

Study	**Ratziu 2011**[804]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=192)
Countries and setting	Conducted in France; Setting: Multi-centre study with 15 participating centres
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	age ≥18 years, increased ALT levels (>50 U/L) on at least three occasions in the 12 months preceding the screening, ALT level >50 U/L measured at screening in the centralised study laboratory, liver biopsy within 18 months of screening showing histologic changes compatible with NASH

Exclusion criteria	>1 normal ALT value in the year prior to screening, presence of steatosis with nonspecific inflammation deemed insufficient for the diagnosis of steatohepatitis by central pathological review, Child-Pugh class B or C cirrhosis, daily alcohol consumption of ≥30 g (men) or ≥20 g (women), other causes of chronic liver disease, secondary NASH, treatment with UDCA within the past 12 months, vitamin E within the past 6 months, glitazones within the past 3 years, newly instituted antihyperglycaemic therapy within 4 months of screening, loss of ≥15% of body weight since liver biopsy, presence of HCC, pregnancy, breastfeeding women
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (IQR): UDCA group: 49.8 (10.2); placebo group: 49.6 (12.6). Gender (M:F): UDCA group: 47/15; placebo group: 48/16. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: Ursodeoxycholic acid. 28-35 mg/kg body weight/day (500-mg film-coated Urso-DS tablets, Axcan Pharma). Duration 12 months. Concurrent medication/care: Patients were encouraged to follow a health a diet and exercise. No specific dietary instructions were given. (n=64) Intervention 2: Placebo. No specific information given.. Duration 12 months. Concurrent medication/care: Patients were encouraged to follow a health a diet and exercise. No specific dietary instructions were given.
Funding	Study funded by industry (Study funded by Axcan Pharma S.A.; principal author is consultant to various pharmaceutical companies)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: URSODEOXYCHOLIC ACID versus PLACEBO

Protocol outcome 1: Liver function tests at ≥3 to <12 months
- Actual outcome for Adults: Percentage of patients with normalised ALT levels at 6 months; Group 1: 8/57, Group 2: 4/61; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥12 months
- Actual outcome for Adults: Mean change of ALT levels at 12 months; Group 1: mean -28.3 % reduction (SD 55); n=53, Group 2: mean -1.6 % reduction (SD 35.4); n=62; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Percentage of patients with normalised ALT levels at 12 months; Group 1: 13/53, Group 2: 3/62; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months

Study	**Razavizade 2013[807]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Iran; Setting: Single-centre study at a gastroenterology clinic
Line of therapy	1st line
Duration of study	Intervention time: 4 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Ultrasound-proven NAFLD, over 18 years old
Exclusion criteria	daily alcohol consumption of >20 g (men) or > 10 g (women), type-I diabetes, heart disease (ischemic or congestive), hepatic disease (viral hepatitis, autoimmune hepatitis, Wilson's disease, hemochromatosis, liver mass lesion), renal disease (serum creatinine concentration of >1.5 mg/dl), any severe co-morbidities, neoplasm, using any medication during the past 3 months, previous treatment (with thiazolidinediones, biguanides, insulin), pregnancy, lactating women
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Metformin: 36.35 (±8.96); Pioglitazone: 34.20 (±6.79). Gender (M:F): Metformin: 31/9; Pioglitazone: 37/3. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Insulin sensitisers - Pioglitazone. 30 mg/day. Duration 4 months. Concurrent medication/care: Lifestyle modification, calorie intake controlled by dietician

	(n=40) Intervention 2: Insulin sensitisers - Metformin. 1 g/day (to reduce side effects patients received 500 mg/day at first, dose was increased to 1 g/day if tolerated well). Duration 4 months. Concurrent medication/care: Lifestyle modification, calorie intake controlled by dietician
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PIOGLITAZONE versus METFORMIN Protocol outcome 1: Liver function tests at ≥3 to <12 months - Actual outcome for Adults: Mean change in ALT levels at 4 months; Group 1: mean -37.52 U/L (SD 40.7); n=40, Group 2: mean -21.75 U/L (SD 38.3); n=40; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean change in AST levels at 4 months; Group 1: mean -13.74 U/L (SD 27.1); n=40, Group 2: mean -10.82 U/L (SD 17.06); n=40; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	**Santos 2003**[831]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Brazil; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Abnormal levels of biochemical markers for more than six months, BMI higher than 25, ALT/AST/GGT levels at least 1.5

	times the upper limit of normal, ultrasonography showing signs of hepatic steatosis
Exclusion criteria	alcohol consumption of more than 40 g per week, decompensated diabetes mellitus, serum cholesterol and triglycerides above 300 mg/dl, continuous intake of hepatotoxic medicines, positive hepatitis B surface antigen (HBsAg), anti-hepatitis C virus antibodies, other concomitant hepatic or recognised systemic disease
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): UDCA group: 38.4 (±8.1); Placebo group: 36.6 (±12.0). Gender (M:F): UDCA group: 14/1; Placebo group: 14/1. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Ursodeoxycholic acid. 10 mg/kg body weight/day (divided into two daily doses). Duration 3 months. Concurrent medication/care: Not reported (n=15) Intervention 2: Placebo. Not reported. Duration 3 months. Concurrent medication/care: Not reported
Funding	Equipment / drugs provided by industry (Zambon Laboratories, Brazil)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: URSODEOXYCHOLIC ACID versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months
- Actual outcome for Adults: Hepatic density at 3 months; Group 1: mean 51.1 (SD 15.9); n=15, Group 2: mean 48.1 (SD 19.8); n=15; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥3 to <12 months
- Actual outcome for Adults: Mean ALT levels at 3 months; Group 1: mean 52.2 U/L (SD 24.4); n=15, Group 2: mean 43.7 U/L (SD 19.4); n=15; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥12 months; Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	Sanyal 2004[835]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in USA; Setting: General clinical research centre at a university hospital
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Biopsy-proven NAFLD prior to randomisation
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	NASH: minimal histologic criteria were the presence of macrovesicular steatosis with 1) one or more of the following findings: cytologic ballooning, Mallory's hyaline, pericellular fibrosis, and 2) varying degrees of inflammation and portal fibrosis.
Exclusion criteria	Age <18 years, diabetes mellitus, cirrhosis, weight gain or loss of >5 lb in the month preceding entry, severe comorbid conditions limiting life expectancy to <1 year, pregnancy, symptomatic gallstone disease, those being considered for or who had bariatric surgery, iatrogenic NASH, concomitant presence of other causes of liver disease (eg hepatitis C), and refusal to give informed consent or have a liver biopsy examination performed.
Recruitment/selection of patients	Recruitment between 2000 and 2002 among patients suspected of NAFLD
Age, gender and ethnicity	Age - Mean (SD): Vit E + pioglitazone 47 (12) v. Vit E alone 46 (13). Gender (M:F): 10/10. Ethnicity: 100% Caucasian
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Combination of 2 pharmacological interventions. Combination of vitamin E (400 IU daily) and pioglitazone (30 mg daily). The vitamin E was given in its natural form. Doses were selected based on the available literature. Higher doses of vitamin E were not used for fear of augmenting the risk for hepatotoxicity with pioglitazone.. Duration 6 months. Concurrent medication/care: All patients were given standardised recommendations about diet and exercise in accordance with the National Heart Lung and Blood Institute guidelines. (n=10) Intervention 2: Vitamin E. 400 IU orally every day. Vitamin E was given in its natural form. Doses were selected based on the available literature. Higher doses of vitamin E were not used for fear of augmenting the risk for hepatotoxicity with pioglitazone.. Duration 6 months. Concurrent medication/care: All patients were given standardised

	recommendations about diet and exercise in accordance with the National Heart Lung and Blood Institute guidelines.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION OF 2 PHARMACOLOGICAL INTERVENTIONS versus VITAMIN E Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months - Actual outcome for Adults: Percent change from baseline for histological outcomes at 6 months; Other: Combination therapy was superior to vitamin E alone in terms of change in degree of steatosis. There were no significant difference in the two arms when comparing cytologic ballooning, Mallory's hyaline, pericellular fibrosis, or portal fibrosis.; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests at ≥3 to <12 months - Actual outcome for Adults: Normalisation of ALT levels at 6 months; Group 1: 9/8, Group 2: 10/10; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	**Shargorodsky 2012[863]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Israel; Setting: Single-centre study at an outpatient clinic
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Ultrasound proven NAFLD
Exclusion criteria	history of unstable angina/myocardial infarction/cerebrovascular accident/major surgery within past 6 months priod to

	study, unbalanced endocrine disease, any disease that might affect absorption of medications, patients with plasma creatinine >1.5 mg/dl, elevation of liver enzymes to more than twice the upper normal limit, electrolyte abnormalities (plasma potassium levels >5.5 mg/dl), patients with unbalanced medical treatment during first 3 months of study, alcohol consumption of more than 20 g/day, viral or autoimmune or drug induced liver disease
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Placebo: 51.9 (±10.9); Placebo: 55.2 (±14.0). Gender (M:F): Metformin: 17/15; Placebo: 14/17. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Insulin sensitisers - Metformin. 850-1700 mg/day, orally. Duration 12 months. Concurrent medication/care: Not reported (n=31) Intervention 2: Placebo. Matching the metformin treatment plan. Duration 12 months. Concurrent medication/care: Not reported
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN versus PLACEBO

Protocol outcome 1: Liver function tests at ≥3 to <12 months
- Actual outcome for Adults: Mean ALT levels at 4 months; Group 1: mean 29.3 U/L (SD 16.2); n=27, Group 2: mean 29.7 U/L (SD 16.3); n=25; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean AST levels at 4 months; Group 1: mean 25.4 U/L (SD 9.7); n=27, Group 2: mean 27.4 U/L (SD 8.3); n=25; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥12 months
- Actual outcome for Adults: Mean ALT levels at 12 months; Group 1: mean 39.2 U/L (SD 21.8); n=19, Group 2: mean 32.1 U/L (SD 20.6); n=22; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean AST levels at 12 months; Group 1: mean 30.6 U/L (SD 11.6); n=19, Group 2: mean 29.3 U/L (SD 12.9); n=22; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12

	months; Progression of NAFLD at ≥12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months

Study	**Sharma 2012[865]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in India; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	patients aged between 18 and 70, ALT >1.2 times the upper limit of normal on three occasions at least 1 month apart in the preceding 6 months, ultrasound showing diffusely echogenic liver suggestive of fatty infiltration of liver, liver biopsy showing steatosis of hepatocytes with necroinflammatory activity, ballooning hepatocytes and/or fibrosis were included for evaluation
Exclusion criteria	alcohol consumption of >20 g per week, evidence of viral or autoimmune hepatitis, primary biliary cirrhosis, biliary obstruction, Wilson's disease, hemochromatosis, decompensated cirrhosis, drug therapy of more than 4 weeks during the previous 6 weeks (amiodarone, tamoxifen, nifedipine, diltiazem, methotrexate, perhexiline, glucocorticoids, oestrogens), pregnancy, insulin therapy
Recruitment/selection of patients	Patients were enrolled consecutively.
Age, gender and ethnicity	Age - Mean (SD): PTX group: 37.3 (±7.2); Pioglitazone group: 40.4 (±9.9). Gender (M:F): PTX group: 7/4; Pioglitazone group: 4/5. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Pentoxifylline. 1200 mg/day in three divided doses, orally. Duration 6 months. Concurrent medication/care: Reduction of calorie intake by 500 kcal/day, modest exercise regularly at least 5 days per week

	(n=30) Intervention 2: Insulin sensitisers - Pioglitazone. 30 mg/day. Duration 6 months. Concurrent medication/care: Reduction of calorie intake by 500 kcal/day, modest exercise regularly at least 5 days per week
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PENTOXIFYLLINE versus PIOGLITAZONE

Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months
- Actual outcome for Adults: Mean fibrosis stage (final value) at 6 months; Group 1: mean 0.91 (SD 0.71); n=24, Group 2: mean 0.9 (SD 0.9); n=22; Fibrosis stage 0-4 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean steatosis stage (final value) at 6 months; Group 1: mean 1.25 (SD 0.86); n=24, Group 2: mean 1 (SD 0.6); n=22; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean ballooning (final value) at 6 months; Group 1: mean 1.16 (SD 0.71); n=24, Group 2: mean 1.09 (SD 0.7); n=22; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean lobular inflammation (final value) at 6 months; Group 1: mean 0.75 (SD 0.6); n=24, Group 2: mean 0.45 (SD 0.4); n=22; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥3 to <12 months
- Actual outcome for Adults: Mean ALT levels at 6 months; Group 1: mean 36.9 IU/L (SD 19.6); n=30, Group 2: mean 34 IU/L (SD 16.1); n=29; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean AST levels at 6 months; Group 1: mean 27.5 IU/L (SD 9.7); n=30, Group 2: mean 27.7 IU/L (SD 9.1); n=29; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥12 months; Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Study	**Shiasi Arani 2014[871]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=128)
Countries and setting	Conducted in Iran

Study	Shiasi Arani 2014[871]
Line of therapy	1st line
Duration of study	Intervention time: 4 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ultrasound
Stratum	Young people and children
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Obese children with NAFLD between ages 4-18 years.
Exclusion criteria	Obese children with history of alcohol consumption, hereditary syndromes associated with obesity, such as prader willi syndrome, pathological obesity, and obese children suffering from chronic diseases.
Recruitment/selection of patients	Patients recruited form Paediatric Clinic of Kashan University of Medical Sciences
Age, gender and ethnicity	Age - Mean (SD): 10 (3.19). Gender (M:F): 57/62. Ethnicity: Not stated
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Extra comments	Matched for sex, age, BMI between randomised groups
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Insulin sensitisers - Metformin. 1g per day. Duration 4 months. Concurrent medication/care: All patients advised the same in terms of diet, exercise and weightloss program during treatment. (n=28) Intervention 2: Insulin sensitisers - Metformin. 1.5g per day. Duration 4 months. Concurrent medication/care: All patients advised the same in terms of diet, exercise and weightloss program during treatment. (n=28) Intervention 3: Vitamin E. 400U per day. Duration 4 months. Concurrent medication/care: All patients advised the same in terms of diet, exercise and weightloss program during treatment. (n=27) Intervention 4: Vitamin E. 800U per day. Duration 4 months. Concurrent medication/care: All patients advised the same in terms of diet, exercise and weightloss program during treatment.
Funding	Academic or government funding (Kashan University of Medical services)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN 1G versus VITAMIN E 400U Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months	

Study	Shiasi Arani 2014[871]
- Actual outcome for Young people and children: Remission of NAFLD at Remission of NAFLD; Group 1: 4/36, Group 2: 11/28; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN 1G versus VITAMIN E 800U Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months - Actual outcome for Young people and children: Remission of NAFLD at Remission of NAFLD; Group 1: 4/36, Group 2: 4/27; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN 1.5G versus VITAMIN E 400U Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months - Actual outcome for Young people and children: Remission of NAFLD at Remission of NAFLD; Group 1: 5/28, Group 2: 11/28; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN 1.5G versus VITAMIN E 800U Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months - Actual outcome for Young people and children: Remission of NAFLD at Remission of NAFLD; Group 1: 5/28, Group 2: 4/27; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months; Liver function tests at ≥3 to <12 months

Study	Shields 2009[873]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=19)
Countries and setting	Conducted in USA; Setting: Single centre study at a military medical centre
Line of therapy	Unclear

Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Biopsy-proven NASH and one of the following: BMI >27 kg/m2, fasting blood sugar between 110 and 125 kg/m2, diagnosis of polycystic ovarian syndrome, metabolic syndrome
Exclusion criteria	Type-I/II diabetes, fasting blood sugar >125 mg/dl, history of alcoholic liver disease, any other known chronic liver disease, renal insufficiency (serum creatinine >1.2), known allergic reaction to metformin, prior use of insulin sensitisers, gastric bypass within 2 years, untreated thyroid disease, coagulopathy, chronic thrombocytpenia, significant alcohol consumption of >20 g/day or >80 g/week during the 2 years prior to study enrolment
Recruitment/selection of patients	Patients were enrolled consecutively
Age, gender and ethnicity	Age - Mean (SD): Placebo group: 44.4 (±12); Metformin group: 50.2 (±9.1). Gender (M:F): Placebo group: 5/5; Metformin group: 8/1. Ethnicity: Placebo group: 1 Hispanic, 5 Caucasian, 4 Asian; Metformin group: 1 Hispanic, 6 Caucasian, 1 Asian, 1 African American
Further population details	1. Extra-hepatic condition: Insulin resistance
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Insulin sensitisers - Metformin. 500 mg/day, dose increased to 1000 mg/d if serum aminotransferases did not show improvement at 3-month follow-up. Duration 12 months. Concurrent medication/care: DASH (Dietary Approaches to Stop Hypertension) diet emphasizing fruit, vegetables and lowering saturated fat and cholesterol; advised to complete 30 mins of aerobic exercise 4x/week (n=10) Intervention 2: Placebo. following metformin treatment plan, dose increased following the same treatment plan as metformin if serum aminotransferases did not show improvement at 3-month follow-up. Duration 12 months. Concurrent medication/care: DASH (Dietary Approaches to Stop Hypertension) diet emphasizing fruit, vegetables and lowering saturated fat and cholesterol; advised to complete 30 mins of aerobic exercise 4x/week
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥12 months

- Actual outcome for Adults: Mean NAFLD activity score at 12 months; Mean Metformin 3.8; placebo 3.4 (p=0.108) NAS 0-8 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean steatosis (final value) at 12 months; Mean Metformin 1.91; placebo 1.58 (p=0.23); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean ballooning (final value) at 12 months; Mean Metformin 1.74; placebo 1.5 (p = 0.967); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean intra-acinar (lobular) inflammation (final value) at 12 months; Mean Metformin 1.36; placebo 1.28 (p=478); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean fibrosis (final value) at 12 months; Mean Metformin 1.56; placebo 1.9 (p=0.447); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests at ≥12 months - Actual outcome for Adults: Mean change in ALT levels at 12 months; Mean change: Metformin -21.5; placebo -40.7 (difference not significant); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean change in AST levels at 12 months; Mean change: Metformin -5.7; placebo -20.1 (Difference not significant); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥3 to <12 months

Study	**Tock 2010[963]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=35)
Countries and setting	Conducted in Brazil; Setting: Single-centre study at a university hospital
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Young people and children

Subgroup analysis within study	Not applicable
Inclusion criteria	Ultrasound-proven NAFLD
Exclusion criteria	identified genetic disease, metabolic or endocrine disease, chronic alcohol consumption (>20 g/day), previous drug utilisation, other causes of chronic liver disease
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 15-19. Gender (M:F): 35/0. Ethnicity: Not reported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Insulin sensitisers - Metformin. 500mg twice per day. Duration 12 months. Concurrent medication/care: Nutritional therapy (weekly dietetics lessons, reduction of food intake to calorie levels recommended by the dietary reference intake for patients with low levels of physical activity of the same age and gender), exercise therapy (60-minute aerobic sessions three times a week), psychological therapy (weekly psychological orientation group sessions) (n=14) Intervention 2: Placebo. Following the metformin treatment plan. Duration 12 months. Concurrent medication/care: Nutritional therapy (weekly dietetics lessons, reduction of food intake to calorie levels recommended by the dietary reference intake for patients with low levels of physical activity of the same age and gender), exercise therapy (60-minute aerobic sessions three times a week), psychological therapy (weekly psychological orientation group sessions)
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN versus PLACEBO

Protocol outcome 1: Liver function tests at ≥3 to <12 months
- Actual outcome for Young people and children: Mean ALT levels at 6 months; Group 1: mean 39.64 U/L (SD 16.35); n=17, Group 2: mean 48.25 U/L (SD 17.36); n=12; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Mean AST levels at 6 months; Group 1: mean 26.78 U/L (SD 6.8); n=17, Group 2: mean 26.75 U/L (SD 9.4); n=12; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥12 months
- Actual outcome for Young people and children: Mean ALT levels at 12 months; Group 1: mean 41.11 U/L (SD 12.48); n=17, Group 2: mean 57.25 U/L (SD 38.01); n=12;

Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Mean AST levels at 12 months; Group 1: mean 28.77 U/L (SD 11.99); n=17, Group 2: mean 33 U/L (SD 16.71); n=12; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months

Study	**TONIC trial: Lavine 2011[561]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=173)
Countries and setting	Conducted in Unknown multicentre; Setting: Multi-centre study with 10 participating university clinics
Line of therapy	Unclear
Duration of study	Intervention + follow up: 96 weeks + 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Young people and children
Subgroup analysis within study	Post-hoc subgroup analysis: Sex, age, race, Hispanic ethnicity, Tanner stage, elevated ALT, presence of NASH, BMI, weight, vitamin E levels, adherence
Inclusion criteria	Biopsy-confirmed NAFLD, children aged 8-17
Exclusion criteria	Diabetes mellitus, cirrhosis, children younger than 8 years, monogenetic inborn errors of metabolism, pregnancy, viral hepatitis, alcohol use, other causes of chronic liver disease
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): 13.1 (±2.4). Gender (M:F): 140/33. Ethnicity: 61.3% Hispanic
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Insulin sensitisers - Metformin. 500 mg twice daily, oral. Duration 96 weeks. Concurrent medication/care: Vitamin E placebo twice daily

	(n=58) Intervention 2: Vitamin E. 400 IU twice daily. Duration 96 weeks. Concurrent medication/care: Metformin placebo twice daily (n=58) Intervention 3: Placebo. Vitamin E placebo twice daily, metformin placebo twice daily. Duration 96 weeks. Concurrent medication/care: None
Funding	Other author(s) funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN versus VITAMIN E

Protocol outcome 1: Quality of life at ≥12 months
- Actual outcome for Young people and children: Mean change in self-reported QOL (physical) at 96 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Mean change in self-reported QOL (psychosocial) at 96 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Mean change in parent/guardian-reported QOL (physical) at 96 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Mean change in parent/guardian-reported QOL (psychosocial) at 96 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of NAFLD at ≥12 months
- Actual outcome for Young people and children: Fibrosis score at 96 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Steatosis score at 96 weeks; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Lobular inflammation score at 96 weeks; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Ballooning degeneration score at 96 weeks; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: NAFLD activity score at 96 weeks; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Resolution of NASH at 96 weeks; Group 1: 16/50, Group 2: 25/50; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Liver function tests at ≥12 months
- Actual outcome for Young people and children: ALT at 96 weeks; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: AST at 96 weeks; Risk of bias: ; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METFORMIN versus PLACEBO

Protocol outcome 1: Quality of life at ≥12 months
- Actual outcome for Young people and children: Mean change in self-reported QOL (physical) at 96 weeks; Group 1: mean 5.4 (SD 16.4); n=51, Group 2: mean 5.4 (SD 21.2); n=49; Pediatric Quality of Life Inventory (version 4.0) 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Mean change in self-reported QOL (psychosocial) at 96 weeks; Group 1: mean 4 (SD 15.6); n=51, Group 2: mean 5.6 (SD 19.5); n=49; Pediatric Quality of Life Inventory (version 4.0) 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Mean change in parent/guardian-reported QOL (physical) at 96 weeks; Group 1: mean 4.1 (SD 28.1); n=51, Group 2: mean 4.8 (SD 21.9); n=49; Pediatric Quality of Life Inventory (version 4.0) 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Mean change in parent/guardian-reported QOL (psychosocial) at 96 weeks; Group 1: mean 1.9 (SD 30); n=51, Group 2: mean 6.1 (SD 20.9); n=49; Pediatric Quality of Life Inventory (version 4.0) 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of NAFLD at ≥12 months
- Actual outcome for Young people and children: Mean change in NAFLD activity score at 96 weeks; Group 1: mean -1.1 U/L (SD 2.1); n=50, Group 2: mean -0.7 U/L (SD 2); n=47; NAS 0-8 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Change in fibrosis score at 96 weeks; Group 1: mean -0.4 (SD 1.0556); n=50, Group 2: mean -0.2 (SD 1.3623); n=47; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Change in steatosis score at 96 weeks; Group 1: mean -0.6 (SD 1.0556); n=50, Group 2: mean -0.4 (SD 1.3623); n=47; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Change in lobular inflammation score at 96 weeks; Group 1: mean -0.4 (SD 0.7037); n=50, Group 2: mean -0.3 (SD 1.0218); n=47; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Change in ballooning degeneration score at 96 weeks; Group 1: mean -0.3 (SD 1.0556); n=50, Group 2: mean 0.1 (SD 0.3406); n=47; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Resolution of NASH at 96 weeks; Group 1: 16/50, Group 2: 11/47; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Liver function tests at ≥3 to <12 months
- Actual outcome for Young people and children: Mean change in ALT levels from baseline at 24 weeks; Group 1: mean -3 U/L (SD 68.2); n=57, Group 2: mean -24.5 U/L (SD 70.4); n=58; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Young people and children: Mean change in ALT levels from baseline at 96 weeks; Group 1: mean -41.7 U/L (SD 79.9); n=57, Group 2: mean -35.2 U/L (SD 82.5); n=58; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Liver function tests at ≥12 months
- Actual outcome for Young people and children: Mean change in AST levels from baseline at 96 weeks; Group 1: mean -21.5 U/L (SD 46.6); n=51, Group 2: mean -20.4 U/L (SD 42.8); n=49; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VITAMIN E versus PLACEBO

Protocol outcome 1: Quality of life at ≥12 months - Actual outcome for Young people and children: Mean change in self-reported QOL (physical) at 96 weeks; Group 1: mean 7.6 (SD 17.2); n=50, Group 2: mean 5.4 (SD 21.2); n=49; Pediatric Quality of Life Inventory (version 4.0) 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Mean change in self-reported QOL (psychosocial) at 96 weeks; Group 1: mean 6 (SD 16.2); n=50, Group 2: mean 5.6 (SD 19.5); n=49; Pediatric Quality of Life Inventory (version 4.0) 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Mean change in parent/guardian-reported QOL (physical) at 96 weeks; Group 1: mean 1.5 (SD 33.1); n=50, Group 2: mean 4.8 (SD 21.9); n=49; Pediatric Quality of Life Inventory (version 4.0) 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Mean change in parent/guardian-reported QOL (psychosocial) at 96 weeks; Group 1: mean 6 (SD 20.8); n=50, Group 2: mean 5.6 (SD 20.9); n=49; Pediatric Quality of Life Inventory (version 4.0) 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of NAFLD at ≥12 months - Actual outcome for Young people and children: Mean change in NAFLD activity score at 96 weeks; Group 1: mean -1.8 (SD 2.1); n=50, Group 2: mean -0.7 (SD 2); n=47; NAS 0-8 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Change in lobular inflammation score at 96 weeks; Group 1: mean -0.3 (SD 0.7037); n=50, Group 2: mean -0.3 (SD 1.0218); n=47; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Change in fibrosis score at 96 weeks; Group 1: mean -0.3 (SD 1.0556); n=50, Group 2: mean -0.2 (SD 1.3623); n=47; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Change in steatosis score at 96 weeks; Group 1: mean -0.8 (SD 1.0556); n=50, Group 2: mean -0.4 (SD 1.3623); n=47; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Change in ballooning degeneration score at 96 weeks; Group 1: mean -0.5 (SD 1.0556); n=50, Group 2: mean 0.1 (SD 0.3406); n=47; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Resolution of NASH at 96 weeks; Group 1: 25/50, Group 2: 11/47; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function tests at ≥3 to <12 months - Actual outcome for Young people and children: Mean change in ALT levels from baseline at 24 weeks; Group 1: mean -49.2 U/L (SD 57.8); n=58, Group 2: mean -24.5 U/L (SD 70.4); n=58; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Young people and children: Mean change in ALT levels from baseline at 96 weeks; Group 1: mean -48.3 U/L (SD 70.4); n=58, Group 2: mean -35.2 U/L (SD 82.5); n=58; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Liver function tests at ≥12 months - Actual outcome for Young people and children: Mean change in AST levels from baseline at 96 weeks; Group 1: mean -22.8 U/L (SD 36.9); n=50, Group 2: mean -20.4 U/L (SD 42.8); n=49; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3

	to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months

Study	**Wagner 2011**[1013]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: Single-centre study at an urban hospital
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Biopsy-proven NASH, informed consent
Exclusion criteria	HIV positive, pregnancy, ongoing alcohol consumption exceeding 20 g (men) or 10 g (women) per day, treatment with drugs known to cause steatohepatitis, current or past history of decompensated liver disease, renal failure, evidence of active bleeding, cerebral or retinal haemorrhaging, various drug treatments (thiazolidinediones, weight loss medications, metfo5rmin, vitamin E, anti-TNFα therapy, theophylline), patients on insulin secretagogues, dose adjustments of lipid lowering drugs/insulin/sulfonylureas within 6 months prior to study period, other forms of liver disease
Recruitment/selection of patients	All patients with NASH attending the clinic from March 2005 to March 2008 were evaluated.
Age, gender and ethnicity	Age - Other: Mean (±SEM): PTX group: 48 (±2); Placebo group: 53 (±2). Gender (M:F): PTX group: 8/13; Placebo group: 6/3. Ethnicity: PTX group: 17 Caucasian, 3 Hispanic, 1 Asian; Placebo group: 7 Caucasian
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Pentoxifylline. 400mg three times per day. Duration 12 months. Concurrent medication/care: Not reported (n=9) Intervention 2: Placebo. Three times per day. Duration 12 months. Concurrent medication/care: Not reported

Funding	Other (Study was supported by investigator initiated funds.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PENTOXIFYLLINE versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥12 months
- Actual outcome for Adults: Mean change in NAFLD activity score at 12 months; Group 1: mean -1.4 (SD 1.7); n=19, Group 2: mean -0.3 (SD 1.1); n=7; NAFLD activity score (NAS) 0-8 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean change in fibrosis score at 12 months; Group 1: mean -0.2 (SD 1.3); n=19, Group 2: mean 0.4 (SD 0.5); n=7; Fibrosis score 0-4 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean change in steatosis grade at 12 months; Group 1: mean -0.8 (SD 0.2); n=19, Group 2: mean -0.6 (SD 0.3); n=7; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean change in lobular inflammation at 12 months; Group 1: mean -0.1 (SD 0.2); n=19, Group 2: mean 0.3 (SD 0.3); n=7; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean change in hepatocyte ballooning at 12 months; Group 1: mean -0.5 (SD 0.2); n=19, Group 2: mean 0 (SD 0.2); n=7; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Liver function tests at ≥12 months
- Actual outcome for Adults: Mean change in ALT levels at 12 months; Group 1: mean -25.1 U/L (SD 44.9); n=19, Group 2: mean -12 U/L (SD 14.3); n=7; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Mean change in AST levels at 12 months; Group 1: mean -20.7 U/L (SD 34.4); n=19, Group 2: mean -10.1 U/L (SD 18); n=7; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Normalisation in ALT levels at 12 months; Group 1: 6/19, Group 2: 1/7; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Normalisation of AST levels at 12 months; Group 1: 5/19, Group 2: 0/7; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥3 to <12 months

Study	**Zein 2011**[1081]
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=55)
Countries and setting	Conducted in USA; Setting: Double-centre study
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Biopsy-proven NASH, daily alcohol intake <30 g (men) or <15 g (women), appropriate exclusion of other liver diseases, between 18 and 70 years old, ability to give informed consent, diabetic patients only included if (1) treatment was limited to oral agents including sulfonylureas and/or biguanides, (2) the disease was stable (no change in treatment for 6 months), (3) HbA1C <8%
Exclusion criteria	history of excessive alcohol drinking for a period longer than 2 years in past 10 years, positive testing for hepatitis B or C, any other suspected liver disease by history or blood test or clinical finding, patients with treatment known to cause steatosis, treatment with medication that has shown benefits in previous NASH pilot studies, cirrhosis defined by stage 4 fibrosis on liver biopsy or by unequivocal clinical evidence consistent with underlying cirrhosis, hypersensitivity to PTX or the methylxanthines, history of cerebral or retinal haemorrhage, patients taking theophylline or Coumadin
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 50 (±11.1). Gender (M:F): 38/17. Ethnicity: 93% White
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Pentoxifylline. 400 mg orally three times per day. Duration 12 months. Concurrent medication/care: Not reported (n=29) Intervention 2: Placebo. Orally three times per day. Duration 12 months. Concurrent medication/care: Not reported
Funding	Academic or government funding (Grants from the National Center for Research Resources, American College of Gastroenterology Junior Faculty Career Development Award)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PENTOXIFYLLINE versus PLACEBO Protocol outcome 1: Progression of NAFLD at ≥12 months - Actual outcome for Adults: Mean change of NAFLD activity score at 12 months; Group 1: mean -1.6 (SD 1.1); n=20, Group 2: mean -0.1 (SD 1.4); n=26; NAFLA activity score (NAS) 0-8 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: NAS decreased by ≥2 points at 12 months; Group 1: 10/20, Group 2: 4/26; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean change of steatosis from baseline at 12 months; Group 1: mean -0.85 (SD 0.6); n=20, Group 2: mean -0.4 (SD 0.7); n=26; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean change of lobular inflammation from baseline at 12 months; Group 1: mean -0.45 (SD 0.7); n=20, Group 2: mean 0.08 (SD 0.8); n=26; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean change ballooning from baseline at 12 months; Group 1: mean -0.25 (SD 0.7); n=20, Group 2: mean -0.15 (SD 0.5); n=26; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Mean change fibrosis from baseline at 12 months; Group 1: mean -0.2 (SD 0.7); n=20, Group 2: mean 0.4 (SD 0.9); n=26; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events at ≥12 months - Actual outcome for Adults: Any side effects at 12 months; Group 1: 11/25, Group 2: 14/28; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Liver function tests at ≥12 months - Actual outcome for Adults: Normalisation or improvement of ≥30% in ALT levels from baseline at 12 months; Group 1: 13/23, Group 2: 6/26; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Normalisation or improvement of ≥30% in AST levels from baseline at 12 months; Other: The difference between treatment groups regarding normalisation or improvement of 30% or more from baseline did not reach statistical significance.; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at ≥3 to <12 months; Quality of life at ≥12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥3 to <12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Liver function tests at ≥3 to <12 months

Study	**Zelber-sagi 2006[1086]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Israel; Setting: Single fatty liver clinic

Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis od NAFLD based on ultrasound-guided liver biopsy (n=40) or ultrasound only (n=4)
Stratum	Adults: Not specified as adults but age range suggests that it is (18-75 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	NAFLD
Exclusion criteria	Patients with a known cause for their increased liver enzyme levels such as viral hepatitis (B or C), autoimmune/chronic immune hepatitis, primary biliary cirrhosis, metabolic and genetic hemochromatosis, Wilson's disease, or alpha-1 antitrypsin deficiency, thytrotoxicosis, consumed alcohol in excess, taking hepatotoxic drugs, ot pregnancy.
Recruitment/selection of patients	January to December 2003
Age, gender and ethnicity	Age - Mean (SD): Orlistat group 48.4 (8.1); Placebo group 47 (12.2). Gender (M:F): 19/25. Ethnicity: Not rerported
Further population details	1. Extra-hepatic condition: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Orlistat. 120 mg 3 times a day. Duration 6 months. Concurrent medication/care: Nutritional therapy based on a balanced low-energy diet prescribed by a nutritionist. Diet included 104.5 kJ/day for ideal body weight, with an emphasis on reduced intake of both fat (≤30% of daily calories) and simple carbohydrates. Patients were encouraged to perform physical activity 2-4 times a week (40mins of walking at 5-6 km/h) (n=26) Intervention 2: Placebo. Placebo tablets supplied by Roche were indistinguishable from the orlistat tablets.. Duration 6 months. Concurrent medication/care: Nutritional therapy based on a balanced low-energy diet prescribed by a nutritionist. Diet included 104.5 kJ/day for ideal body weight, with an emphasis on reduced intake of both fat (≤30% of daily calories) and simple carbohydrates. Patients were encouraged to perform physical activity 2-4 times a week (40mins of walking at 5-6 km/h)
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORLISTAT versus PLACEBO

Protocol outcome 1: Progression of NAFLD at ≥3 to <12 months

- Actual outcome for Adults: Ultrasound assessed reversal of fatty liver: percentage of group with normal echogenicity at 6 months; Group 1: 5/21, Group 2: 4/23; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Histopathologically assessed decrease in steatosis: number of patients with improved grading at 6 months; Group 1: 2/11, Group 2: 4/11; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults: Histopathologically assessed at least one degree of improvement of fibrosis at 6 months; Group 1: 5/11, Group 2: 3/11; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Liver function tests at ≥3 to <12 months - Actual outcome for Adults: Decrease in ALT level from baseline at 6 months; Group 1: mean 30.6 U/L (SD 59); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Decrease in AST level from baseline at 6 months; Group 1: mean 18.9 U/L (SD 33); n=21, Group 2: mean 8.8 U/L (SD 17.2); n=23; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Quality of life at ≥3 to <12 months; Mortality at ≥12 months; Mortality at ≥3 to <12 months; Progression of NAFLD at ≥12 months; Serious adverse events at ≥12 months; Serious adverse events at ≥3 to <12 months; Adverse events at ≥3 to <12 months; Adverse events at ≥12 months; Liver function tests at ≥12 months

Appendix I: Economic evidence tables

I.1 Diagnosing the severity of NAFLD

Study	Crossan 2015[226]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: cost analysis (cost per additional correct diagnosis) **Study design:** decision tree **Approach to analysis:** Proportion of true and false outcomes of testing using the 2 strategies were calculated based on their diagnostic accuracy. **Perspective:** UK healthcare provider **Time horizon**: NA **Discounting:** Costs: NA; Outcomes: NA	**Population:** People with NAFLD with suspected liver fibrosis	Detailed results in the full guideline: Table 31 and Table 32, Section 7.4.1		Detailed results in the full guideline: Table 31 and Table 32, Section 7.4.1 **Analysis of uncertainty:** No sensitivity analysis conducted. No confidence intervals reported.
Data sources				
Health outcomes: Diagnostic accuracy data were extracted from papers following a systematic literature review. **Cost sources:** Costs of imaging tests were sourced from Department of Health reference costs. Liver biopsy costs were extracted from a previous NIHR HTA (Stevenson 2012).[918] Costs of serum markers were based on personal communications with NHS hospitals and test manufacturers.				
Comments				
Source of funding: National Institute for Health Research. **Limitations:** No costs or health outcomes following diagnosis were considered in the model. The time horizon is not long enough to capture all the effects, no sensitivity analysis conducted and no confidence interval were reported.				
Overall applicability[(a)]: partially applicable **Overall quality[(b)]:** potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years.
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Steadman 2013[915]			
Study details	**Population &**	**Costs**	**Health outcomes**	**Cost-effectiveness**

	interventions			
Economic analysis: cost analysis (cost per additional correct diagnosis) **Study design:** decision tree **Approach to analysis:** Proportion of true and false outcomes of testing using the 2 strategies were calculated based on their diagnostic accuracy. Separate results reported for fibrosis stage ≥F2 and stage=F4 (only ≥F2 presented here as F4 not relevant). **Perspective:** Canadian healthcare provider **Time horizon:** NA **Discounting:** Costs: NA; Outcomes: NA	**Population:** Meta-analysis of published diagnostic accuracy studies People with NAFLD and fibrosis. Age: 48 years Males: 59% **Intervention 1:** Transient elastography **Intervention 2:** Liver biopsy	**Total costs (mean per patient):** Intervention 1: £56 Intervention 2: £261 Incremental (2−1): £205 (95% CI: NR; p=NR) **Currency & cost year:** 2010 Canadian dollars (presented here as 2010 UK pounds[(a)]) **Cost components incorporated:** Only test costs considered	**Correct diagnoses (per 1000 patient):** Intervention 1: 758 Intervention 2: 1000 [(b)] Incremental (2−1): 242 (95% CI: NR; p=NR)	**Cost per additional correct diagnosis (Intervention 2 versus Intervention 1):** £846 (95% CI: £277 to £2237) **Analysis of uncertainty:** Changes in sensitivity, specificity and prevalence have a significant effect on the resulting cost per correct diagnosis
Data sources				
Health outcomes: Pooled diagnostic accuracy data were obtained from 5 studies. **Cost sources:** Liver biopsy costs were obtained from a single Canadian study, transient elastography costs were estimated through a microcosting process.				
Comments				
Source of funding: Funded by Alberta Health. **Limitations:** Differences in healthcare system may make results less applicable to UK, no health outcomes following diagnosis were considered in the model. Transient elastography diagnostic accuracy estimates were informed by observational data. **Other:** The study reported results for fibrosis stage ≥F2 and stage=F4 of the METAVIR classification scale. For the purpose of the report only fibrosis stage ≥F2 is presented here. The study also reported for 4 additional patient subgroups with HBV, HCV, cholestatic liver disease, and post-liver transplantation.				
Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations				

Abbreviations: da: deterministic analysis; HBV: Hepatitis; HCV: Hepatitis C; NAFLD: non-alcoholic fatty liver disease; 95% CI: 95% confidence interval; NA: not applicable

(a) Converted using 2010 purchasing power parities[719]

(b) The economic model assumed that the sensitivity and specificity of liver biopsy is equal to 1 (reference standard)

(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

I.2 Pharmacological interventions

Study	**Mahady 2012[620]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov decision model **Approach to analysis:** • Annual cycle length • Health states reflecting disease progression: NASH, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplantation **Perspective:** Payer perspective (direct healthcare costs) **Time horizon:** Lifetime **Treatment effect duration[(a)]:** Lifetime **Discounting:** 5% for costs and benefits	**Population:** Biopsy-proven NASH with fibrosis F3–F4 patients with no prior treatment **Cohort settings:** Start age: 50 years Male: NA **Intervention 1 – lifestyle modification:** Hepatologist review with diet and exercise recommendations twice per year and annual consultation with dietitian **Intervention 2 – vitamin E:** Daily oral dose of 536 mg (800 IU[(b)]) in addition to lifestyle advice (intervention 1)[(c)] **Intervention 3 - pioglitazone:** Daily oral dose of 30 mg in addition to lifestyle modification advice (intervention 1)[(c)]	**Total costs (mean per patient):** Intervention 1: £21,108 Intervention 2: £23,403 Intervention 3: £27,074 Incremental (2−1): £2,295 (95% CI: NR; p=NR) Incremental (3−1): £5,966 (95% CI: NR; p=NR) Incremental (3−2): £3,671 (95% CI: NR; p=NR) **Currency & cost year:** 2010 Australian dollars (presented here as 2010 UK pounds)[(d)] **Cost components incorporated:** Annual clinical care costs for every health state. Itemised costs for: consultation costs, pathology costs, drugs, radiology and procedures	**QALYs (mean per patient):** Intervention 1: 6.26 Intervention 2: 6.85 Intervention 3: 10.99 Incremental (2−1): 0.59 (95% CI: NR; p=NR) Incremental (3−1): 4.73 (95% CI: NR; p=NR) Incremental (3−2): 4.14 (95% CI: NR; p=NR)	**ICER** Intervention 2 is extendedly dominated (that is, a combination of Interventions 1 and 3 is both cheaper and more effective). Intervention 3 versus Intervention 1**:** £1261.31 per QALY gained (da) 95% CI: NR Probability intervention 3 is cost-effective (£20K/30K threshold): NR/NR **Analysis of uncertainty:** No probabilistic sensitivity analysis was performed. In the 2-way sensitivity analysis and across a range of probabilities of 2–6% per year for the development of cirrhosis, pioglitazone remained cost-effective compared to lifestyle modification until its annual cost was greater than £7342 (base case was £778). Vitamin E remained cost-effective compared to lifestyle modification irrespective of cohort starting age and until extreme cost limits. When the likelihood for people with advanced fibrosis to develop cirrhosis was less than 2% per year, then neither vitamin E nor pioglitazone were cost-effective compared to lifestyle modification.

Data sources
Health outcomes: Derived from a systematic literature review, other published sources and a NAFLD patient database. **Quality-of-life weights:** 2 out of 9 utility values were based on authors' assumptions. The remaining utilities were derived from other causes of chronic liver disease than NAFLD/NASH. **Cost sources:** Resource use was mainly based on authors' assumptions, unit costs were obtained from various sources, believed to reflect Australian practice.
Comments
Source of funding: NR. **Limitations:** Differences in healthcare system may make results less applicable to UK; some utility values based on authors' assumptions; utility values were obtained from other causes of chronic liver disease. Resource use based on authors' assumptions, no probabilistic analysis conducted.
Overall applicability[(e)]: partially applicable **Overall quality[(f)]:** potentially serious limitations

Abbreviations % CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; IU: international units; NR: not reported; QALYs: quality-adjusted life years; NASH: non-alcoholic steatohepatitis

(a) Treatment assumed to continue with equal effectiveness until onset of decompensated cirrhosis or death. Effectiveness of either drug is not known over very long treatment duration.

(b) 1 IU of alpha-tocopherol was assumed to be equivalent to 0.67 mg of vitamin E in natural form.

(c) Both drugs were stopped if patients developed decompensated liver disease, as they have not been tested in this stage.

(d) Converted using 2010 purchasing power parities[719]

(e) Directly applicable / Partially applicable / Not applicable

(f) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix J: GRADE tables

J.1 Dietary modification and supplements

Table 16: Clinical evidence profile: probiotics versus placebo or usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotic versus placebo or usual care	Control	Relative (95% CI)	Absolute		
NAFLD progression; MRS hepatic triglyceride content (adults), <12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	10	10	-	MD 6.8 lower (13.59 to 0.01 lower)	⊕⊕⊕O MODERATE	CRITICAL
NAFLD progression; transient elastography fibrosis score (adults), <12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	26	-	MD 2.21 lower (3 to 1.42 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
ALT (U/l) (adults), <12 months (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	50	-	MD 17.68 lower (20.13 to 15.24 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
ALT (U/l) (children / young people), <12 months (follow-up 2-6 months; Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	44	-	MD 17.66 lower (26.89 to 8.43 lower)	⊕⊕⊕O MODERATE	IMPORTANT
AST (U/l) (adults), <12 months (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	very serious[3]	no serious indirectness	no serious imprecision	none	50	50	-	MD 21.01 lower (24.04 to 17.97 lower)	⊕⊕OO LOW	IMPORTANT
Weight loss (BMI) (adults), <12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	14	14	-	MD 3.6 higher (14.8 to 7.6 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Weight loss (BMI) (children / young people), <12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	34	-	MD 0.8 lower (1.6 lower to 0 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Any adverse event (adults), <12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/10 (40%)	4/10 (40%)	RR 1 (0.34 to 2.93)	0 fewer per 1000 (from 264 fewer to	⊕⊕OO LOW	IMPORTANT

										772 more)		
Serious adverse event (adults), <12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/26 (0%)	0%	-	-	⊕⊕⊕O MODERATE	IMPORTANT

1 Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs.

2 Downgraded by one increment if the majority of evidence was at high risk of bias or two increments if the majority of evidence was at very high risk of bias.

3 Heterogeneity, I2=91, p<0.0001.

Table 17: Clinical evidence profile: omega-3 fatty acids versus placebo or usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Omega 3 fatty acids**	**Control**	**Relative (95% CI)**	**Absolute**		
NAFLD progression; MRS liver fat (%) (adults), ≥12 months (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	68	69	-	MD 3.56 lower (6.86 to 0.27 lower)	⊕⊕OO LOW	CRITICAL
NAFLD progression; liver fibrosis score (adults), ≥12 months (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	51	52	-	MD 0.1 higher (0.43 lower to 0.63 higher)	⊕OOO VERY LOW	CRITICAL
NAFLD progression; composite of NAS ≥3/fibrosis unchanged and/or NAS decrease ≥2/ fibrosis unchanged (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	43/119 (36.1%)	22/55 (40%)	RR 0.9 (0.6 to 1.35)	40 fewer per 1000 (from 160 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
NAFLD progression; NAS ≥3/fibrosis unchanged (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	38/119 (31.9%)	20/55 (36.4%)	RR 0.88 (0.57 to 1.36)	44 fewer per 1000 (from 156 fewer to 131 more)	⊕⊕OO LOW	CRITICAL
NAFLD progression; NAS decrease ≥2/ fibrosis unchanged (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	34/119 (28.6%)	18/55 (32.7%)	RR 0.87 (0.54 to 1.4)	43 fewer per 1000 (from 151 fewer to 131 more)	⊕⊕OO LOW	CRITICAL
NAFLD progression; MRI hepatic fat fraction (children / young people), <12 months (follow-up mean 6 months; % decrease - better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	25	26	-	MD 30.8 higher (6.22 to 55.38 higher)	⊕⊕⊕O MODERATE	CRITICAL
ALT (U/l) (adults), <12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	18	18	-	MD 16 lower (31.71 to 0.29 lower)	⊕⊕OO LOW	IMPORTANT
ALT (U/l) (adults), ≥12 months (Better indicated by lower values)												
2	randomised	no serious	no serious	no serious	no serious	none	68	69	-	MD 2.39 lower (12.39	⊕⊕⊕⊕	IMPORTANT

	trials	risk of bias	inconsistency	indirectness	imprecision					lower to 7.6 higher)	HIGH	
ALT (U/l) (children / young people), <12 months (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25	26	-	MD 18 lower (28.08 to 7.92 lower)	⊕⊕⊕O MODERATE	IMPORTANT
AST (U/l) (adults), <12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	18	18	-	MD 0.2 higher (5.42 lower to 5.82 higher)	⊕⊕⊕O MODERATE	IMPORTANT
AST (U/l) (adults), ≥12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	52	-	MD 4.1 higher (4.6 lower to 12.8 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Weight (kg) (adults) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	17	17	-	MD 4.9 higher (8.43 lower to 18.23 higher)	⊕⊕OO LOW	IMPORTANT
Weight reduction (children / young people), 6 months (follow-up median 6 months; assessed with: >5% reduction)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/30 (16.7%)	20.6%	RR 0.81 (0.29 to 2.28)	39 fewer per 1000 (from 146 fewer to 264 more)	⊕⊕OO LOW	IMPORTANT
BMI (children / young people), <12 months (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	25	26	-	MD 0.1 higher (2.53 lower to 2.73 higher)	⊕⊕⊕O MODERATE	IMPORTANT
BMI reduction (children / young people), 6 months (follow-up median 6 months; assessed with: >5% reduction)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	12/30 (40%)	14.7%	RR 2.72 (1.08 to 6.83)	253 more per 1000 (from 12 more to 857 more)	⊕⊕⊕O MODERATE	IMPORTANT
Any adverse event (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	140/168 (83.3%)	71/75 (94.7%)	RR 0.88 (0.81 to 0.96)	114 fewer per 1000 (from 38 fewer to 180 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Any adverse event (children and young people), mild abdominal discomfort, 6 months (follow-up median 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/30 (3.3%)	2.9%	RR 1.13 (0.07 to 17.34)	4 more per 1000 (from 27 fewer to 474 more)	⊕⊕OO LOW	IMPORTANT
Serious adverse events (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	13/168 (7.7%)	5/75 (6.7%)	RR 1.16 (0.43 to 3.14)	11 more per 1000 (from 38 fewer to 143 more)	⊕⊕OO LOW	IMPORTANT
Severe adverse event (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	23/168 (13.7%)	7/75 (9.3%)	RR 1.47 (0.66 to 3.27)	44 more per 1000 (from 32 fewer to 212 more)	⊕⊕OO LOW	IMPORTANT

1 Downgraded by one increment if the majority of evidence was at high risk of bias or two increments if the majority of evidence was at very high risk of bias.

2 Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 increment due to indirect intervention (omega 3 fatty acid intervention was not purified).

J.2 Exercise interventions

Table 18: Clinical evidence profile: exercise versus control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	Control	Relative (95% CI)	Absolute		
NAFLD progression; MRS intrahepatic lipid CH2-water / intrahepatic triglyceride (%); RCT (Better indicated by lower values)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43	32	-	MD 2.67 lower (4.87 to 0.46 lower)	⊕OOO VERY LOW	CRITICAL
NAFLD progression; liver biopsy NAS (range 0 to 8); RCT (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9	11	-	MD 0.4 lower (1.76 lower to 0.96 higher)	⊕OOO VERY LOW	CRITICAL
ALT levels (U/l); RCT (Better indicated by lower values)												
6	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	83	72	-	MD 3.07 lower (7.03 lower to 0.9 higher)	⊕OOO VERY LOW	IMPORTANT
AST levels (U/l); RCT (Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27	27	-	MD 5.56 lower (12.88 lower to 1.76 higher)	⊕OOO VERY LOW	IMPORTANT
Weight (kg); RCT - Aerobic exercise (Better indicated by lower values)												
2	randomised trials	very serious[1]	very serious[3]	no serious indirectness	very serious[2]	none	18	11	-	MD 3.65 lower (21.63 lower to 14.33 higher)	⊕OOO VERY LOW	IMPORTANT
Weight (kg); RCT - High intensity exercise (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12	11	-	MD 1.6 lower (11.26 lower to 8.06 higher)	⊕OOO VERY LOW	IMPORTANT
Weight (kg); RCT - Resistance exercise (Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44	39	-	MD 0.71 lower (1.36 to 0.06 lower)	⊕⊕OO LOW	IMPORTANT

1 Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs.
3 Heterogeneity, I2=74%, p=0.05, unexplained by subgroup analysis.

J.3 Lifestyle modification

Table 19: Lifestyle modification (any diet plus any exercise plus behavioural modification) versus control (usual care) (RCTs) <12 months

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lifestyle modification versus control (RCT) (<12 months)	Control	Relative (95% CI)	Absolute		
NAS (0-8, final value) (follow-up 48 weeks; range of scores: 0-8; Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	18	10	-	MD 0.5 lower (1.3 lower to 0.3 higher)	⊕⊕OO LOW	CRITICAL
Fat (0-3, final value) (follow-up 48 weeks; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	18	10	-	MD 0 higher (0.64 lower to 0.64 higher)	⊕OOO VERY LOW	CRITICAL
Parenchymal inflammation (0-3, final value)) (follow-up 48 weeks; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	18	10	-	MD 0.3 lower (0.87 lower to 0.27 higher)	⊕⊕OO LOW	CRITICAL
Balooning injury (0-2, final value) (follow-up 48 weeks; range of scores: 0-2; Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	18	10	-	MD 0.1 lower (0.49 lower to 0.29 higher)	⊕OOO VERY LOW	CRITICAL
Fibrosis (0-4, final value) (follow-up 48 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised	Serious[a]	no serious	no serious	Serious[b]	none	18	10	-	MD 0.3 lower (1.01	⊕⊕OO	CRITICAL

	trials		inconsistency	indirectness						lower to 0.41 higher)	LOW	

Table 20: Lifestyle modification (any diet plus any exercise plus behavioural modification) versus control (usual care) (RCTs) ≥12 months

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lifestyle modification versus control (RCT)	Control	Relative (95% CI)	Absolute		
ALT (U/l) (final value) (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	77	77	-	MD 7 lower (11.78 to 2.22 lower)	⊕⊕OO LOW	IMPORTANT
AST (U/l) (final value) (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	77	77	-	MD 0 higher (2.53 lower to 2.53 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Intrahepatic triglyceride (%) (^{1}H-MRS, final value) (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	77	77	-	MD 4.6 lower (6.59 to 2.61 lower)	⊕⊕OO LOW	CRITICAL
Liver stiffness (kPa) (ultrasound, final value) (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	77	77	-	MD 0.6 lower (1.13 to 0.07 lower)	⊕⊕OO LOW	CRITICAL
Body weight (kg) (final value) (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	77	77	-	MD 2.8 lower (6.11 lower to 0.51 higher)	⊕⊕OO LOW	IMPORTANT

Table 21: Lifestyle modification (any diet plus any exercise plus behavioural modification) versus control (usual care) (cohort studies)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lifestyle modification versus control (Cohort)	Control	Relative (95% CI)	Absolute		
ALT (IU/L) (final values) (Better indicated by lower values)												
1	observational studies	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	109	43	-	MD 7 lower (17.5 lower to 3.5 higher)	⊕OOO VERY LOW	CRITICAL
AST (IU/L) (final values) (Better indicated by lower values)												
1	observational studies	very serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	109	43	-	MD 1 lower (3.72 lower to 1.72 higher)	⊕OOO VERY LOW	CRITICAL
NAFLD prevalence (ultrasound) (follow-up 12 months; assessed with: ultrasound)												
1	observational studies	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/109 (50.5%)	40/43 (93%)	RR 0.54 (0.44 to 0.66)	428 fewer per 1000 (from 316 fewer to 521 fewer)	⊕OOO VERY LOW	CRITICAL

Table 22: Diet and exercise versus control (usual care) (RCTs)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet and exercise versus control (RCT)	Control	Relative (95% CI)	Absolute		
ALT (U/l) (change scores) - Low fat diet and moderate exercise versus control (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	12	11	-	MD 23.2 lower (50.99 lower to 4.59 higher)	⊕⊕OO LOW	IMPORTANT
ALT (U/l) (change scores) - Moderate fat fiet and moderate exercise versus control (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	9	11	-	MD 15.5 lower (58.04 lower to 27.04 higher)	⊕OOO VERY LOW	IMPORTANT
AST (U/l) (change scores) - Low fat diet and moderate exercise (Better indicated by lower values)												

1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	12	11	-	MD 13 lower (31.69 lower to 5.69 higher)	⊕⊕OO LOW	IMPORTANT
AST (U/l) (change scores) - Moderate fat diet and moderate exercise (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	9	11	-	MD 16.7 lower (51.51 lower to 18.11 higher)	⊕⊕OO LOW	IMPORTANT
NAS (0-8) (change score) - Low fat diet and moderate exercise (range of scores: 0-8; Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	12	11	-	MD 0.9 lower (2.05 lower to 0.25 higher)	⊕⊕OO LOW	CRITICAL
NAS (0-8) (change score) - Moderate fat diet and moderate exercise (range of scores: 0-8; Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	9	11	-	MD 0.8 lower (1.9 lower to 0.3 higher)	⊕⊕OO LOW	CRITICAL
Body weight (kg) - Low fat diet and moderate exercise (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	12	11	-	MD 2.3 higher (2.08 lower to 6.68 higher)	⊕⊕OO LOW	IMPORTANT
Body weight (kg) - Moderate fat diet and moderate exercise (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	9	11	-	MD 0.5 lower (4.89 lower to 3.89 higher)	⊕OOO VERY LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 23: Diet and exercise versus control (combination of usual care and no control group details given) (cohort study)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet and exercise versus control (Cohort)	Control	Relative (95% CI)	Absolute		

ALT (U/l) (final values) (Better indicated by lower values)												
2	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	31	25	-	MD 36.69 lower (88.37 lower to 14.98 higher)	⊕OOO VERY LOW	IMPORTANT
AST (U/l) (final values) (Better indicated by lower values)												
2	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	26	25	-	MD 29.18 lower (68.99 lower to 10.64 higher)	⊕OOO VERY LOW	IMPORTANT
NAFLD progression with fibroscan (0-3 severity scale, final values) (range of scores: 0-3; Better indicated by lower values)												
1	observational studies	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	16	15	-	MD 0.53 lower (0.95 to 0.11 lower)	⊕OOO VERY LOW	IMPORTANT
Body weight (%) (Better indicated by lower values)												
1	observational studies	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	16	15	-	MD 6.03 lower (15.33 lower to 3.27 higher)	⊕OOO VERY LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 24: Diet and exercise versus exercise (RCTs)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diet and exercise versus exercise (RCT)**	**Control**	**Relative (95% CI)**	**Absolute**		
ALT (U/l) (change scores) (Better indicated by lower values)												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	18	-	MD 3.56 lower (25.21 lower to 18.09 higher)	⊕⊕OO LOW	IMPORTANT
AST (U/l) (change scores) (Better indicated by lower values)												
1	randomised	very	no serious	no serious	serious[2]	none	21	18	-	MD 8.01 lower (19.87	⊕OOO	IMPORTANT

	trials	serious[a]	inconsistency	indirectness						lower to 3.85 higher)	VERY LOW	
NAFLD activity score (0–8) (change score) (range of scores: 0–8; Better indicated by lower values)												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	21	18	-	MD 0.45 lower (1.26 lower to 0.36 higher)	⊕OOO VERY LOW	CRITICAL
Body weight (kg) (change scores) (Better indicated by lower values)												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	21	18	-	MD 1.7 lower (4.8 lower to 1.4 higher)	⊕⊕OO LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 25: Diet and exercise versus exercise (cohort study

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diet and exercise versus Exercise (Cohort)**	**Control**	**Relative (95% CI)**	**Absolute**		
ALT (IU/) (final value) (Better indicated by lower values)												
1	observational studies	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	16	23	-	MD 10.78 lower (24.18 lower to 2.62 higher)	⊕OOO VERY LOW	IMPORTANT
AST (U/l) (final values) (Better indicated by lower values)												
1	observational studies	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	16	23	-	MD 4.87 lower (10.34 lower to 0.6 higher)	⊕OOO VERY LOW	IMPORTANT
Body weight (kg) final values) (Better indicated by lower values)												
1	observational studies	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	16	23	-	MD 5.85 lower (14.11 lower to 2.41 higher)	⊕OOO VERY LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 26: Diet and exercise versus diet (RCTs)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet and exercise versus diet (RCT)	Control	Relative (95% CI)	Absolute		
ALT (U/l) (final values) (Better indicated by lower values)												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	50	-	MD 14.63 lower (16.92 to 12.34 lower)	⊕⊕OO LOW	IMPORTANT
AST (U/l) (final values) (Better indicated by lower values)												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	50	-	MD 12.51 lower (14.97 to 10.05 lower)	⊕⊕OO LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

J.4 Pharmacological interventions

Table 27: Clinical evidence profile: Pioglitazone versus placebo for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pioglitazone versus Placebo	Control	Relative (95% CI)	Absolute		
Adverse events (cardiovascular) >12 months (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/80 (12.5%)	14.5%	RR 0.86 (0.4 to 1.89)	20 fewer per 1000 (from 87 fewer to 129 more)	⊕OOO VERY LOW	IMPORTANT
Decrease in fibrosis >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/31 (29%)	20%	RR 1.45 (0.59 to 3.58)	90 more per 1000 (from 82 fewer to 516	⊕⊕OO LOW	CRITICAL

										more)		
Improvement in fibrosis >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35/70 (50%)	31.3%	RR 1.38 (0.94 to 2.04)	119 more per 1000 (from 19 fewer to 326 more)	⊕⊕OO LOW	CRITICAL
Decrease in hepatocellular injury >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	10/31 (32.3%)	10%	RR 3.23 (0.98 to 10.59)	223 more per 1000 (from 2 fewer to 959 more)	⊕⊕⊕O MODERATE	CRITICAL
Improvement in hepatocellular ballooning >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35/70 (50%)	28.9%	RR 1.5 (1 to 2.24)	145 more per 1000 (from 0 more to 358 more)	⊕⊕OO LOW	CRITICAL
Decrease in lobular inflammation >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	14/31 (45.2%)	26.7%	RR 1.69 (0.83 to 3.44)	184 more per 1000 (from 45 fewer to 651 more)	⊕⊕⊕O MODERATE	CRITICAL
Improvement in lobular inflammation >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/70 (68.6%)	34.9%	RR 1.7 (1.23 to 2.35)	244 more per 1000 (from 80 more to 471 more)	⊕⊕OO LOW	CRITICAL
Decrease in Mallory-Denk bodies >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	8/31 (25.8%)	3.3%	RR 7.74 (1.03 to 58.21)	222 more per 1000 (from 1 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Decrease in portal inflammation >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/31 (25.8%)	23.3%	RR 1.11 (0.46 to 2.67)	26 more per 1000 (from 126 fewer to 389 more)	⊕⊕OO LOW	CRITICAL
Decrease in steatosis score >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	15/31 (48.4%)	36.7%	RR 1.32 (0.73 to 2.39)	117 more per 1000 (from 99 fewer to 510 more)	⊕⊕OO LOW	CRITICAL
Increase in fibrosis >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/31 (0%)	20%	OR 0.11 (0.02 to 0.58)	200 fewer per 1000 (from 350 fewer to 50 fewer)[3]	⊕⊕⊕⊕ HIGH	CRITICAL
Increase in hepatocellular injury >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	4/31 (12.9%)	40%	RR 0.32 (0.12 to 0.89)	272 fewer per 1000 (from 44 fewer to 352 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Increase in lobular inflammation >12 months (follow-up 12 months; assessed with: Histology (Brunt))												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/31 (12.9%)	10%	RR 1.29 (0.31 to 5.29)	29 more per 1000 (from 69 fewer to 429 more)		CRITICAL
Increase in Mallory-Denk bodies >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/31 (0%)	10%	OR 0.12 (0.01 to 1.22)	100 fewer per 1000 (from 219 fewer to 19 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Increase in portal inflammation >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/31 (25.8%)	36.7%	RR 0.7 (0.33 to 1.5)	110 fewer per 1000 (from 246 fewer to 184 more)	⊕⊕OO LOW	CRITICAL
Increase in steatosis score >12 months (follow-up 12 months; assessed with: Histology (Brunt))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/31 (3.2%)	10%	RR 0.32 (0.04 to 2.93)	68 fewer per 1000 (from 96 fewer to 193 more)	⊕⊕OO LOW	CRITICAL
Improvement in steatosis >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious imprecision	none	55/70 (78.6%)	31.3%	RR 2.18 (1.56 to 3.03)	369 more per 1000 (from 175 more to 635 more)	⊕⊕⊕O MODERATE	CRITICAL	no serious imprecision
Reduction in fibrosis score of ≥2, ≥3 to <12 months (follow-up 6 months; assessed with: Histology (Kleiner))												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/12 (41.7%)	16.7%	RR 2.5 (0.37 to 16.89)	251 more per 1000 (from 105 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Reduction in steatosis score of ≥2, ≥3 to <12 months (follow-up 6 months; assessed with: Histology (Kleiner))												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/21 (42.9%)	0%	OR 8.84 (1.92 to 40.63)	428.6 more per 1000 (from 202.5 more to 654.6 more)[3]	⊕⊕OO LOW	CRITICAL
Improvement in ballooning necrosis ≥3 to <12 months (follow-up 6 months; assessed with: Histology (Kleiner))												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/26 (53.8%)	23.8%	RR 2.26 (0.97 to 5.26)	300 more per 1000 (from 7 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Improvement in fibrosis ≥3 to <12 months (follow-up 6 months; assessed with: Histology (Kleiner))												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/26 (46.2%)	33.3%	RR 1.38 (0.66 to 2.88)	127 more per 1000 (from 113 fewer to 626 more)	⊕OOO VERY LOW	CRITICAL
Improvement in lobular inflammation ≥3 to <12 months (follow-up 6 months; assessed with: Histology (Kleiner))												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/26 (65.4%)	28.6%	RR 2.29 (1.1 to 4.76)	369 more per 1000 (from 29 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Improvement in histologic features of the liver >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27/70 (38.6%)	19.3%	RR 1.74 (1.03 to 2.93)	143 more per 1000 (from 6 more to 372	⊕⊕OO LOW	CRITICAL

										more)		
Resolution of definite NASH >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/70 (54.3%)	20.5%	RR 2.3 (1.44 to 3.76)	266 more per 1000 (from 90 more to 566 more)	⊕⊕⊕O MODERATE	CRITICAL
Severe adverse events >12 months (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/80 (2.5%)	12.1%	RR 0.21 (0.05 to 0.92)	96 fewer per 1000 (from 10 fewer to 115 fewer)	⊕⊕OO LOW	CRITICAL
ALT levels >12 months (final values) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	37	-	MD 21.3 lower (37.44 to 5.16 lower)	⊕⊕OO LOW	IMPORTANT
ALT levels ≥3 to <12 months (final values) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	21	-	MD 12 lower (20.61 to 3.39 lower)	⊕OOO VERY LOW	IMPORTANT
AST levels ≥3 to <12 months (final values) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	21	-	MD 5 lower (10.05 lower to 0.05 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] ARD calculated manually due to single study with zero events in 1 arm.

Table 28: Clinical evidence profile: Metformin versus placebo for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Metformin versus Placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Proportion with Improvement in ballooning necrosis score ≥3 to <12 months (follow-up 12-31 months; assessed with: Histology (NAS))												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/20 (5%)	12.5%	RR 0.4 (0.05 to 3.55)	75 fewer per 1000 (from 119 fewer to 319 more)	⊕OOO VERY LOW	CRITICAL
Proportion with Improvement in fibrosis score ≥3 to <12 months (follow-up 12-31 months; assessed with: Histology (NAS))												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/20 (5%)	16.7%	RR 0.3 (0.04 to 2.47)	117 fewer per 1000 (from 160 fewer to 245 more)	⊕OOO VERY LOW	CRITICAL
Proportion with Improvement in lobular inflammation score ≥3 to <12 months (follow-up 12-31 months; assessed with: Histology (NAS))												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/20 (15%)	33.3%	RR 0.45 (0.14 to 1.47)	183 fewer per 1000 (from 286 fewer to 157 more)	⊕OOO VERY	CRITICAL

											LOW	
Proportion with Improvement in NAFLD activity score ≥3 to <12 months (follow-up 12-31 months; assessed with: Histology (NAS))												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/20 (20%)	50%	RR 0.4 (0.15 to 1.05)	300 fewer per 1000 (from 425 fewer to 25 more)	⊕⊕OO LOW	CRITICAL
Proportion with Improvement in steatosis ≥3 to <12 months (follow-up 12-31 months; assessed with: Histology (NAS))												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/20 (25%)	37.5%	RR 0.67 (0.27 to 1.67)	124 fewer per 1000 (from 274 fewer to 251 more)	⊕OOO VERY LOW	CRITICAL
Final ALT levels >12 months (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	22	-	MD 7.1 higher (5.95 lower to 20.15 higher)	⊕OOO VERY LOW	IMPORTANT
Final AST levels >12 months (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19	22	-	MD 1.3 higher (6.2 lower to 8.8 higher)	⊕OOO VERY LOW	IMPORTANT
Final ALT levels ≥3 to <12 months (follow-up 4 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	27	25	-	MD 0.4 lower (9.24 lower to 8.44 higher)	⊕OOO VERY LOW	IMPORTANT
Final AST levels ≥3 to <12 months (follow-up 4 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27	25	-	MD 2 lower (6.9 lower to 2.9 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 29: Clinical evidence profile: Metformin versus placebo for NAFLD (children)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Metformin versus Placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
AST levels >12 moths - Change scores (follow-up mean 96 weeks; measured with: Serology ; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	49	-	MD 1.1 lower (18.63 lower to 16.43 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
AST levels >12 moths - Final value (follow-up mean 12 months; measured with: serology; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17	12	-	MD 4.23 lower (15.27 lower to 6.81 higher)	⊕OOO VERY LOW	IMPORTANT
ALT levels >12 months - Change score (follow-up mean 96 weeks; measured with: Serology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	58	-	MD 6.5 lower (36.18 lower to 23.18 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
ALT levels >12 months - Final values (follow-up mean 12 months; measured with: Serology; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17	12	-	MD 16.14 lower (38.45 lower to 6.17 higher)	⊕OOO VERY LOW	IMPORTANT
ALT levels ≥3 to <12 months - Change score (follow-up mean 96 weeks; measured with: Serology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	57	58	-	MD 21.5 higher (3.83 lower to 46.83 higher)	⊕⊕⊕O MODERATE	IMPORTANT
ALT levels ≥3 to <12 months - Final value (follow-up mean 12 months; measured with: Serology; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17	12	-	MD 8.61 lower (21.14 lower to 3.92 higher)	⊕OOO VERY LOW	IMPORTANT
AST levels ≥3 to <12 months (final value) (follow-up mean 12 months; measured with: Serology; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17	12	-	MD 0.03 higher (6.19 lower to 6.25 higher)	⊕OOO VERY LOW	IMPORTANT
Ballooning degeneration score >12 months (change score) (follow-up mean 96 weeks; measured with: Histological scoring system ; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	50	47	-	MD 0.4 lower (0.71 to 0.09 lower)	⊕⊕OO LOW	CRITICAL
Fibrosis score >12 weeks (change scores) (follow-up mean 96 weeks; measured with: Histology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	47	-	MD 0.2 lower (0.69 lower to 0.29 higher)	⊕⊕⊕O MODERATE	CRITICAL
Lobular inflammation score >12 months (change score) (follow-up mean 96 weeks; measured with: Histology ; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	47	-	MD 0.1 lower (0.45 lower to 0.25 higher)	⊕⊕⊕O MODERATE	CRITICAL
Steatosis score >12 months (change score) (follow-up mean 96 weeks; measured with: Histology; Better indicated by lower values)												
1	randomised	no serious risk of	no serious	no serious	serious[2]	none	50	47	-	MD 0.2 lower	⊕⊕⊕O	CRITICAL

	trials	bias	inconsistency	indirectness						(0.69 lower to 0.29 higher)	MODERATE	
NAFLD activity score >12 months (change score) (follow-up mean 96 weeks; measured with: composite score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	47	-	MD 0.4 lower (1.22 lower to 0.42 higher)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of NASH >12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	16/50 (32%)	23.4%	RR 1.37 (0.71 to 2.64)	87 more per 1000 (from 68 fewer to 384 more)	⊕⊕OO LOW	CRITICAL
Parent reported paediatric QoL Inventory (physical, 0-100) >12 months (change score) (follow-up mean 96 weeks; measured with: paediatric QoL Inventory; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	49	-	MD 0.7 lower (10.55 lower to 9.15 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Self-reported paediatric QoL Inventory (physical, 0-100) >12 months (change score) (follow-up mean 96 weeks; measured with: paediatric QoL Inventory ; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	49	-	MD 0 higher (7.45 lower to 7.45 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Parent reported paediatric QoL Inventory (psychosocial, 0-100) >12 months (change score) (follow-up mean 96 weeks; measured with: paediatric QoL Inventory ; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	51	49	-	MD 4.2 lower (14.3 lower to 5.9 higher)	⊕⊕⊕O MODERATE	CRITICAL
Self-reported paediatric QoL Inventory (psychosocial, 0-100) >12 months (change score) (follow-up mean 96 weeks; measured with: paediatric QoL Inventory ; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	49	-	MD 1.6 lower (8.54 lower to 5.34 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs.

Table 30: Clinical evidence profile: Vitamin E versus placebo for NAFLD (adults)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin E versus Placebo	Control	Relative (95% CI)	Absolute		
Adverse events (cardiovascular) >12 months (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/84 (14.3%)	14.5%	RR 0.99 (0.47 to 2.07)	1 fewer per 1000 (from 77 fewer to 155 more)	⊕OOO VERY LOW	IMPORTANT
Mortality >12 months (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/84 (1.2%)	0%	OR 7.3 (0.14 to 368)	12 more per 1000 (from 21 fewer to 44 more)[3]	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/84 (8.3%)	12.1%	RR 0.6 (0.28 to 1.73)	48 fewer per 1000 (from 87 fewer to 88 more)	⊕OOO VERY LOW	IMPORTANT
Improvement in histologic features of the liver >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/80 (45%)	19.3%	RR 2.02 (1.23 to 3.32)	197 more per 1000 (from 44 more to 448 more)	⊕⊕⊕O MODERATE	CRITICAL
Improvement in steatosis >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/80 (56.3%)	31.3%	RR 1.56 (1.08 to 2.24)	175 more per 1000 (from 25 more to 388 more)	⊕⊕OO LOW	CRITICAL
Improvement in lobular inflammation >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/80 (56.3%)	34.9%	RR 1.56 (1.08 to 2.24)	195 more per 1000 (from 28 more to 433 more)	⊕⊕OO LOW	CRITICAL
Improvement in hepatocellular ballooning >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	42/80 (52.5%)	34.9%	RR 1.3 (0.92 to 1.85)	105 more per 1000 (from 28 fewer to 297 more)	⊕⊕OO LOW	CRITICAL
Improvement in fibrosis >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/80 (42.5%)	31.3%	RR 1.18 (0.79 to 1.75)	56 more per 1000 (from 66 fewer to 235 more)	⊕⊕OO LOW	CRITICAL
Resolution of definite NASH >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/80 (37.5%)	17/72 (23.6%)	RR 1.56 (0.96 to 2.63)	132 more per 1000 (from 9 fewer to 385 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] ARD calculated manually due to single study with zero events in one arm

Table 31: Clinical evidence profile: Vitamin E versus placebo for NAFLD (children)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin E versus Placebo	Control	Relative (95% CI)	Absolute		
AST levels (change score) >12 months (follow-up mean 96 weeks; measured with: Serology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	49	-	MD 2.4 lower (18.16 lower to 13.36 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
ALT levels (change score) ≥3 to <12 months (follow-up mean 96 weeks; measured with: serology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	58	58	-	MD 24.7 lower (48.14 to 1.26 lower)	⊕⊕⊕O MODERATE	IMPORTANT
ALT levels (change score) >12 months (follow-up mean 96 weeks; measured with: Serology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	58	58	-	MD 13.1 lower (41.01 lower to 14.81 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Ballooning degeneration score >12 months (follow-up mean 96 weeks; measured with: Histology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	47	-	MD 0.61 lower (0.92 to 0.3 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Fibrosis score (0-4, change score) >12 months (follow-up mean 96 weeks; measured with: Histology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	47	-	MD 0.1 lower (0.59 lower to 0.39 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Lobular inflammation score (0-2, change score) >12 months (follow-up mean 96 weeks; measured with: Histology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	47	-	MD 0 higher (0.35 lower to 0.35 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Steatosis score (0-4, change score) >12 months (follow-up mean 96 weeks; measured with: Histology; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	47	-	MD 0.4 lower (0.89 lower to 0.09 higher)	⊕⊕⊕O MODERATE	CRITICAL
NAFLD activity score (0-8, change score) >12 months (follow-up mean 96 weeks; measured with: composite score ; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	47	-	MD 1.1 lower (1.92 to 0.28 lower)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of NASH >12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	25/50 (50%)	23.4%	RR 2.14 (1.19 to 3.84)	267 more per 1000 (from 44 more to 665 more)	⊕⊕⊕O MODERATE	CRITICAL
Parent-reported QoL (physical, 0-100, change score) >12 months (follow-up mean 96 weeks; measured with: QoL scale; Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	49	-	MD 3.3 lower (14.34 lower to 7.74 higher)	⊕⊕⊕O MODERATE	CRITICAL
Parent-reported QoL (psychosocial, 0-100, change score) >12 months (follow-up mean 96 weeks; measured with: QoL scale; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	49	-	MD 0.4 higher (7.81 lower to 8.61 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Self-reported QoL (physical, 0-100, change score) >12 months (follow-up mean 96 weeks; measured with: QoL scale; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	49	-	MD 2.2 higher (5.41 lower to 9.81 higher)	⊕⊕⊕O MODERATE	CRITICAL
Self-reported QoL (psychosocial, 0-100, change score) >12 months (follow-up mean 96 weeks; measured with: QoL scale; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	49	-	MD 0.4 higher (6.67 lower to 7.47 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs.

Table 32: Clinical evidence profile: UDCA versus placebo for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UDCA versus Placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Normalised ALT levels >12 months (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/53 (24.5%)	4.8%	RR 5.07 (1.53 to 16.84)	195 more per 1000 (from 25 more to 760 more)	⊕⊕⊕O MODERATE	IMPORTANT
Normalised ALT levels ≥3 to <12 months (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/57 (14%)	6.6%	RR 2.14 (0.68 to 6.72)	75 more per 1000 (from 21 fewer to 378 more)	⊕⊕OO LOW	IMPORTANT
ALT levels >12 months (change score) (follow-up 12-24 months; Better indicated by lower values)												
3	randomised trials	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	203	214	-	MD 11.07 lower (28.32 lower to 6.17 higher)	⊕⊕OO LOW	IMPORTANT
AST levels >12 months (change score) (follow-up 18-24 months; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	149	155	-	MD 1.74 lower (12.33 lower to 8.84 higher)	⊕⊕OO LOW	IMPORTANT
ALT levels ≥3 to <12 months (final value) (follow-up 3 months; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 8.5 higher (7.28 lower to 24.28 higher)	⊕OOO VERY LOW	IMPORTANT
Steatosis (0-4) >12 months (final value) (follow-up 2 years; measured with: Histology (NAS); range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14	13	-	MD 0.1 higher (0.81 lower to 1.01 higher)	⊕⊕OO LOW	CRITICAL
NAFLD activity score (0-8) >12 months (change score) (follow-up 18 months; measured with: Histology (NAS); range of scores: 0-8; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69	68	-	MD 0.19 lower (0.62 lower to 0.24 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change in ballooning >12 months (change score) (follow-up 18 months; measured with: Histology (NAS); Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69	68	-	MD 0.09 higher (0.09 lower to 0.27 higher)	⊕⊕⊕O MODERATE	CRITICAL
Fibrosis (0-3) >12 months (change score) (follow-up 18-24 months; measured with: Histology (NAS/Brunt); range of scores: 0-3; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	119	123	-	MD 0.05 lower (0.18 lower to 0.08 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change in lobular inflammation >12 months (change score) (measured with: Histology (NAS); Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	69	68	-	MD 0.23 lower (0.43 to 0.03 lower)	⊕⊕OO LOW	CRITICAL
Change in steatosis >12 months (change score) (follow-up 18-24 months; measured with: Histology (NAS/Brunt); Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	119	125	-	MD 0.07 lower (0.23 lower to 0.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Hepatic density ≥3 to <12 months (change score) (follow-up 3 months; measured with: CT; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15	15	-	MD 3 higher (9.85 lower to 15.85 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because heterogeneity, I2=57%, p=0.10. Sub-grouping by extra hepatic conditions not possible due to insufficient data reported by included papers.

Table 33: Clinical evidence profile: Pentoxifylline versus placebo for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pentoxifylline versus Placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Adverse events >12 months (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11/25 (44%)	50%	RR 0.88 (0.49 to 1.57)	60 fewer per 1000 (from 255 fewer to 285 more)	⊕⊕OO LOW	IMPORTANT
Normalisation in ALT levels >12 months (follow-up 12 months)												

2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	19/42 (45.2%)	18.7%	RR 2.4 (1.15 to 5.02)	262 more per 1000 (from 28 more to 752 more)	⊕⊕OO LOW	IMPORTANT
Normalisation of AST levels >12 months (follow-up 12 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	19/42 (45.2%)	18.7%	OR 9.65 (1.23 to 75.43)	500 more per 1000 (from 160 more to 840 more)[3]	⊕OOO VERY LOW	IMPORTANT
NAFLD activity score decreased by ≥2 points >12 months (follow-up 12 months; assessed with: Histology (NAS))												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	10/20 (50%)	15.4%	RR 3.25 (1.19 to 8.86)	347 more per 1000 (from 29 more to 1000 more)	⊕⊕OO LOW	CRITICAL
ALT levels (change score) >12 months (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	19	7	-	MD 13.1 lower (35.9 lower to 9.7 higher)	⊕⊕OO LOW	IMPORTANT
AST levels (change score) >12 months (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	19	7	-	MD 10.6 lower (31.02 lower to 9.82 higher)	⊕⊕OO LOW	IMPORTANT
ALT levels (final value) ≥3 to <12 months (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11	9	-	MD 24.71 lower (49.21 to 0.21 lower)	⊕⊕⊕O MODERATE	IMPORTANT
AST levels (final values) ≥3 to <12 months (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11	9	-	MD 16.15 lower (29.33 to 2.97 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Hepatocyte ballooning (change score) >12 months (follow-up 12 months; measured with: Histology (NAS); Better indicated by lower values)												
2	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[1]	none	39	33	-	MD 0.33 lower (0.72 lower to 0.05 higher)	⊕⊕OO LOW	CRITICAL
Lobular inflammation (change score) >12 months (follow-up 12 months; measured with: Histology (NAS); Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	39	33	-	MD 0.43 lower (0.64 to 0.22 lower)	⊕⊕⊕O MODERATE	CRITICAL
NAFLD activity score (0-8, change score) >12 months (follow-up 12 months; measured with: Histology (NAS); Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	33	-	MD 1.38 lower (1.99 to 0.78 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in steatosis (change score) >12 months (follow-up 12 months; measured with: Histology (NAS); Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	33	-	MD 0.27 lower (0.47 to 0.07 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in fibrosis (change score) >12 months (follow-up 12 months; measured with: Histology (NAS); Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	33	-	MD 0.6 lower (0.78 to 0.42 lower)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[3] ARD calculated manually due to single study with zero events in one arm
[4] Downgraded by 1 or 2 increments because heterogeneity, I2=74%, p=0.045. Sub-group analysis not possible due to insufficient information reported in included papers.

Table 34: Clinical evidence profile: Statins versus placebo for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins versus placebo	Control	Relative (95% CI)	Absolute		
ALT levels (final values) >12 months (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10	6	-	MD 25.8 lower (48.67 to 2.93 lower)	⊕OOO VERY LOW	IMPORTANT
AST levels (final value) >12 months (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10	6	-	MD 12.8 lower (23.22 to 2.38 lower)	⊕OOO VERY LOW	IMPORTANT
Fibrosis stage (final score) >12 months (follow-up 12 months; measured with: Histology; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	6	-	MD 0.5 higher (0.75 lower to 1.75 higher)	⊕OOO VERY LOW	CRITICAL
Percentage Steatosis (final value) >12 months (follow-up 12 months; measured with: Histology; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	6	-	MD 3.8 higher (17.66 lower to 25.26 higher)	⊕OOO VERY LOW	CRITICAL
Necroinflammatory activity >12 months (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	6	-	MD 0.4 higher (0.76 lower to 1.56 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 35: Clinical evidence profile: Orlistat versus placebo for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Orlistat	Control	Relative	Absolute		

studies						considerations	versus Placebo		(95% CI)			
≥1 degree improvement in fibrosis ≥3 to <12 months (follow-up 6 months; assessed with: Histopathology (Brunt))												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/11 (45.5%)	27.3%	RR 1.67 (0.52 to 5.33)	183 more per 1000 (from 131 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Improved steatosis ≥3 to <12 months (follow-up 6 months; assessed with: Histopathology (Brunt))												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/11 (18.2%)	36.4%	RR 0.5 (0.11 to 2.19)	182 fewer per 1000 (from 324 fewer to 433 more)	⊕OOO VERY LOW	CRITICAL
Reversal of fatty liver ≥3 to <12 months (follow-up 6 months; assessed with: ultrasound (% with normal echogenicity))												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/21 (23.8%)	17.4%	RR 1.37 (0.42 to 4.43)	64 more per 1000 (from 101 fewer to 597 more)	⊕OOO VERY LOW	CRITICAL
ALT levels (change score) >12 months (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	21	23	-	MD 17.9 lower (45.38 lower to 9.58 higher)	⊕⊕⊕O MODERATE	IMPORTANT
AST levels (change score) >12 months (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	21	23	-	MD 10.1 lower (25.87 lower to 5.67 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 36: Clinical evidence profile: Pioglitazone versus Metformin for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pioglitazone versus Metformin**	**Control**	**Relative (95% CI)**	**Absolute**		
ALT levels >12 months (change score) (follow-up 4 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40	40	-	MD 15.77 lower (33.09 lower to 1.55 higher)	⊕⊕⊕O MODERATE	IMPORTANT
AST levels >12 months (change score) (follow-up 4 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40	40	-	MD 2.92 lower (12.84 lower to 7 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 37: Clinical evidence profile: Pioglitazone versus Vitamin E for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pioglitazone versus Vitamin E	Control	Relative (95% CI)	Absolute		
Adverse events (cardiovascular) >12 months (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/80 (12.5%)	14.3%	RR 0.88 (0.4 to 1.91)	17 fewer per 1000 (from 86 fewer to 130 more)	⊕OOO VERY LOW	IMPORTANT
Mortality >12 months (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/80 (0%)	1.2%	OR 0.14 (0 to 7.16)	12 fewer per 1000 (from 45 fewer to 21 more)[3]	⊕OOO VERY LOW	CRITICAL
Severe adverse events >12 months (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/80 (2.5%)	8.3%	RR 0.3 (0.06 to 1.4)	58 fewer per 1000 (from 78 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL
Improvement in histologic features of the liver >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27/70 (38.6%)	42.9%	RR 0.86 (0.58 to 1.26)	60 fewer per 1000 (from 180 fewer to 112 more)	⊕⊕OO LOW	CRITICAL
Improvement in steatosis >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	55/70 (78.6%)	53.6%	RR 1.4 (1.11 to 1.76)	214 more per 1000 (from 59 more to 407 more)	⊕⊕OO LOW	CRITICAL
Improvement in lobular inflammation >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/70 (68.6%)	53.6%	RR 1.22 (0.95 to 1.57)	118 more per 1000 (from 27 fewer to 306 more)	⊕⊕OO LOW	CRITICAL
Improvement in hepatocellular ballooning >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	35/70 (50%)	50%	RR 0.95 (0.7 to 1.3)	25 fewer per 1000 (from 150 fewer to 150 more)	⊕⊕OO LOW	CRITICAL
Improvement in fibrosis >12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35/70 (50%)	40.5%	RR 1.18 (0.83 to 1.66)	73 more per 1000 (from 69 fewer to 267 more)	⊕⊕OO LOW	CRITICAL
Resolution of definite NASH >12 months												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38/70 (54.3%)	35.7%	RR 1.45 (1.01 to 2.07)	161 more per 1000 (from 4 more to 382 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] ARD calculated manually due to single study with zero events in one arm.

Table 38: Clinical evidence profile: Metformin versus Vitamin E for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Metformin versus Vitamin E**	**Control**	**Relative (95% CI)**	**Absolute**		
Normalised ALT levels >12 months (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	13/29 (44.8%)	14.3%	RR 3.14 (1.16 to 8.47)	306 more per 1000 (from 23 more to 1000 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 39: Clinical evidence profile: Metformin versus Vitamin E for NAFLD (children)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Metformin versus Vitamin E**	**Control**	**Relative (95% CI)**	**Absolute**		
Fibrosis score (change score) >12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	50	-	MD 0.1 lower (0.51 lower to 0.31 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Steatosis score (change score) >12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	50	-	MD 0.2 higher (0.21 lower to	⊕⊕⊕O MODERATE	CRITICAL

										0.61 higher)		
Lobular inflammationscore (change score) >12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	50	-	MD 0.1 higher (0.18 lower to 0.38 higher)	⊕⊕⊕O MODERATE	CRITICAL
Ballooning degeneration score (change score) >12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	50	-	MD 0.2 higher (0.21 lower to 0.61 higher)	⊕⊕⊕O MODERATE	CRITICAL
NAFLD activity score (change score) >12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	50	-	MD 0.7 higher (0.13 lower to 1.53 higher)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of NASH >12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	16/50 (32%)	50%	RR 0.64 (0.39 to 1.04)	180 fewer per 1000 (from 305 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
Remission of NAFLD (ultrasound), Metformin 1g >12 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/72 (11.1%)	15/55 (27.3%)	RR 0.41 (0.19 to 0.9)	161 fewer per 1000 (from 27 fewer to 221 fewer)	⊕OOO VERY LOW	CRITICAL
Remission of NAFLD (ultrasound), Metformin 1.5g >12 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/72 (13.9%)	15/55 (27.3%)	RR 0.51 (0.25 to 1.05)	134 fewer per 1000 (from 205 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
Self-reported paediatric QoL Inventory (physical, 0-100) >12 months (change score) (range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	51	50	-	MD 2.2 lower (8.76 lower to 4.36 higher)	⊕⊕⊕O MODERATE	CRITICAL
Self-reported paediatric QoL Inventory (psychosocial, 0-100) >12 months (change score) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	51	50	-	MD 2 lower (10.57 lower to 6.57 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Parent-reported paediatric QoL Inventory (physical, 0-100) >12 months (change score) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	51	50	-	MD 2.6 higher (9.38 lower to 14.58 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Parent-reported paediatric QoL Inventory (psychosocial, 0-100) >12 months (change score) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	51	50	-	MD 2.4 lower (10.54 lower to 5.74 higher)	⊕⊕⊕O MODERATE	CRITICAL
ALT levels (change score) >12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	51	50	-	MD 6.6 higher (20.85 lower to 34.05 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
AST levels (change score) >12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	51	50	-	MD 1.3 higher (15.08 lower to 17.68 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events ≥3 to <12 months (follow-up mean 6 months; assessed with: adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/22 (9.1%)	0%	peto odds ratio	91 more per 1000 (from 49	⊕⊕OO LOW	IMPORTANT

									8.11 (0.49 to 133.96)	fewer to 204 more)		
Change in triglycerides ≥3 to <12 months (change score) (follow-up mean 6 months; measured with: serology; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	23	-	MD 11 higher (16.68 lower to 38.68 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 40: Clinical evidence profile: Pentoxifylline versus Pioglitazone for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pentoxifylline versus Pioglitazone**	**Control**	**Relative (95% CI)**	**Absolute**		
Hepatocellular ballooning (final value) ≥3 to <12 months (follow-up 6 months; measured with: Histology (Brunt); Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	22	-	MD 0.07 higher (0.34 lower to 0.48 higher)	⊕⊕OO LOW	CRITICAL
Fibrosis stage (final value) ≥3 to <12 months (follow-up 6 months; measured with: Histology (Brunt); Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24	22	-	MD 0.01 higher (0.46 lower to 0.48 higher)	⊕OOO VERY LOW	CRITICAL
Lobullular inflammation (final value) ≥3 to <12 months (follow-up 6 months; measured with: Histology (Brunt); Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	22	-	MD 0.3 higher (0.01 to 0.59 higher)	⊕⊕OO LOW	CRITICAL
Steatosis stage (final value) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	22	-	MD 0.25 higher (0.18 lower to 0.68 higher)	⊕⊕OO LOW	CRITICAL
ALT levels (final value) ≥3 to <12 months (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	29	-	MD 2.9 higher (6.24 lower to 12.04 higher)	⊕⊕OO LOW	IMPORTANT
AST levels (final value) ≥3 to <12 months (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	29	-	MD 0.2 lower (5 lower to 4.6 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 41: Clinical evidence profile: UDCA plus vitamin E versus UDCA for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UDCA + vitamin E versus UDCA	Control	Relative (95% CI)	Absolute		
Steatosis (0-4, final value) >12 months (follow-up 2 years; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14	14	-	MD 1.2 lower (2.17 to 0.23 lower)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 42: Clinical evidence profile: UDCA plus vitamin E versus placebo for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UDCA + vitamin E versus placebo	Control	Relative (95% CI)	Absolute		
Steatosis (0-4, final value) >12 months (follow-up 2 years; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14	13	-	MD 1.1 lower (2.16 to 0.04 lower)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 43: Clinical evidence profile: orlistat plus vitamin E versus vitamin E for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Orlistat + vitamin E versus vitamin E	Control	Relative (95%	Absolute		

									CI)			
ALT levels (final values) ≥3 to <12 months (follow-up 36 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	18	-	MD 15 higher (5.62 lower to 35.62 higher)	⊕OOO VERY LOW	IMPORTANT
AST levels (final values) ≥3 to <12 months (follow-up 36 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	18	-	MD 4 higher (7.93 lower to 15.93 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 44: Clinical evidence profile: pioglitazone plus vitamin E versus vitamin E for NAFLD (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pioglitazone + vitamin E versus vitamin E**	**Control**	**Relative (95% CI)**	**Absolute**		
Normalisation of ALT levels ≥3 to <12 months (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/10 (90%)	100%	RR 0.9 (0.69 to 1.18)	100 fewer per 1000 (from 310 fewer to 180 more)	⊕⊕OO LOW	IMPORTANT

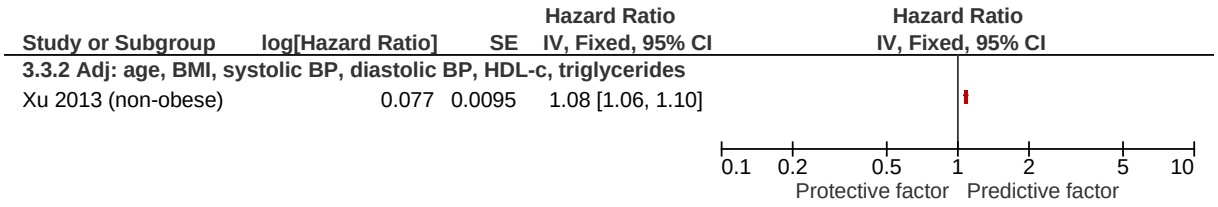
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MID

Appendix K: Forest plots and diagnostic meta-analysis plots

K.1 Risk factors for NAFLD

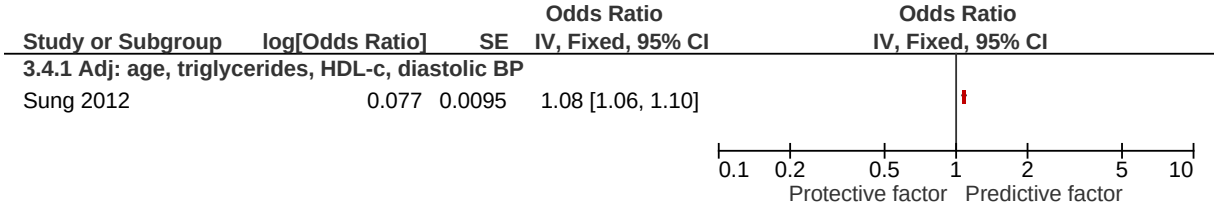
K.1.1.1 Waist circumference

Figure 15: Waist circumference as a prognostic risk factor for NAFLD (Hazard ratio) (adults)



Waist circumference- dichotomous factor (no details)

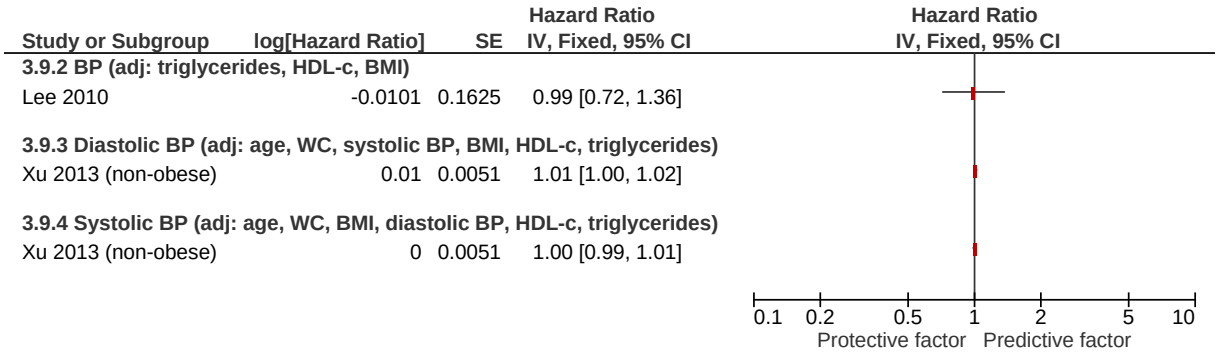
Figure 16: Waist circumference as a prognostic risk factor for NAFLD (Odds ratio) (adults)



Waist circumference: continuous factor

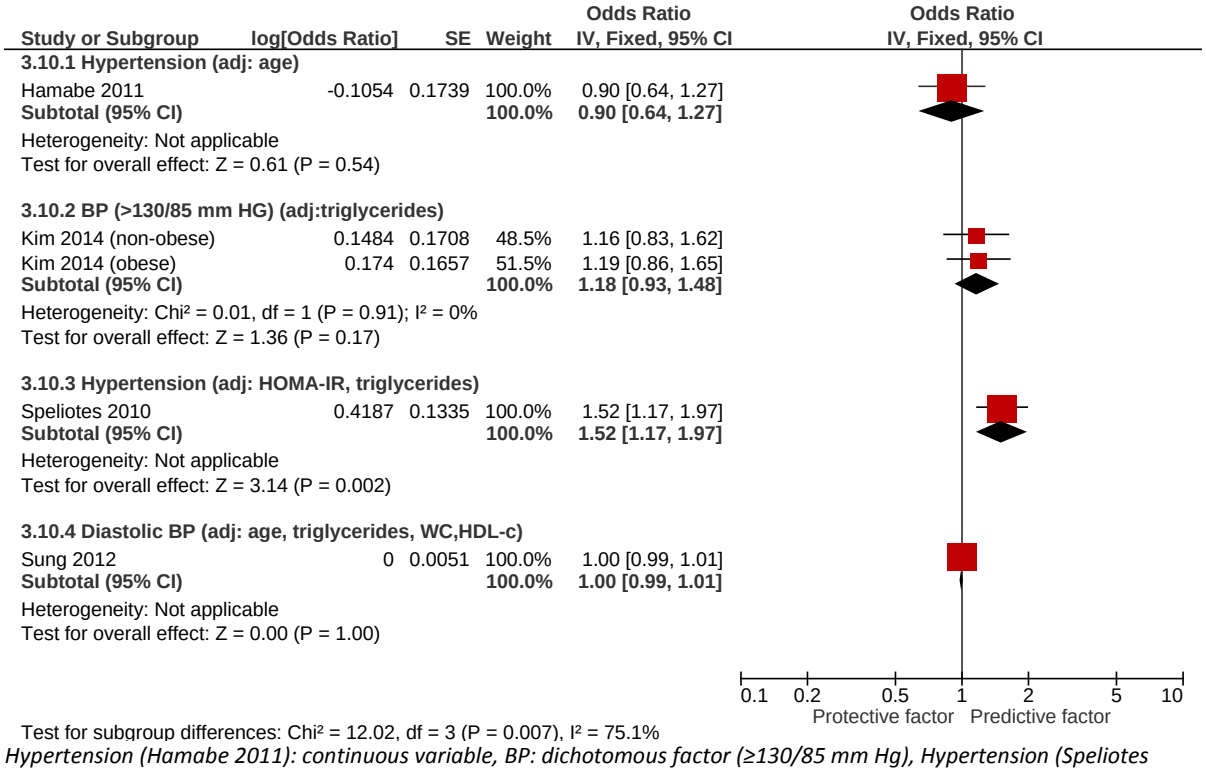
K.1.1.2 Hypertension

Figure 17: Hypertension as a risk factor for NAFLD (Hazard ratio) (adults)



BP: dichotomous factor (≥130/85 mm Hg), diastolic BP: dichotomous factor (no details), systolic BP: dichotomous factor (no details)

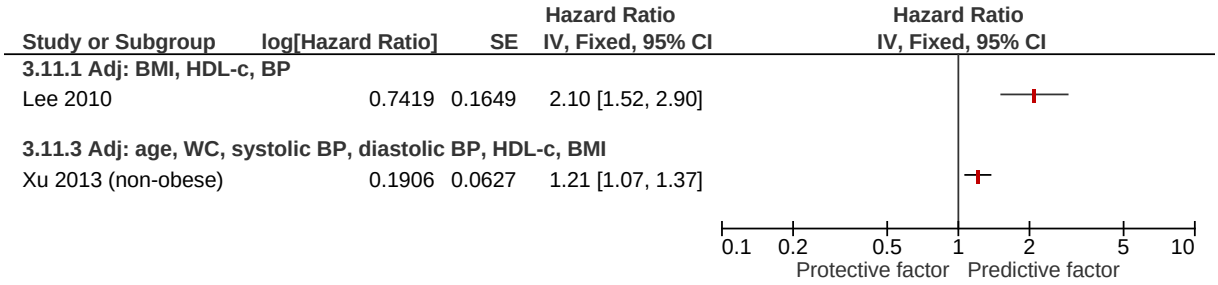
Figure 18: Hypertension as a risk factor for NAFLD (Odds ratio) (adults



Hypertension (Hamabe 2011): continuous variable, BP: dichotomous factor (≥130/85 mm Hg), Hypertension (Speliotes 2010) sdichotomous SBP >140 mmHg/DBP ≥90 mmHg), Sung-continuous factor

1K.1.1.3 Triglycerides

Figure 19: Triglycerides as a risk factor for NAFLD (Hazard ratio) (adults)

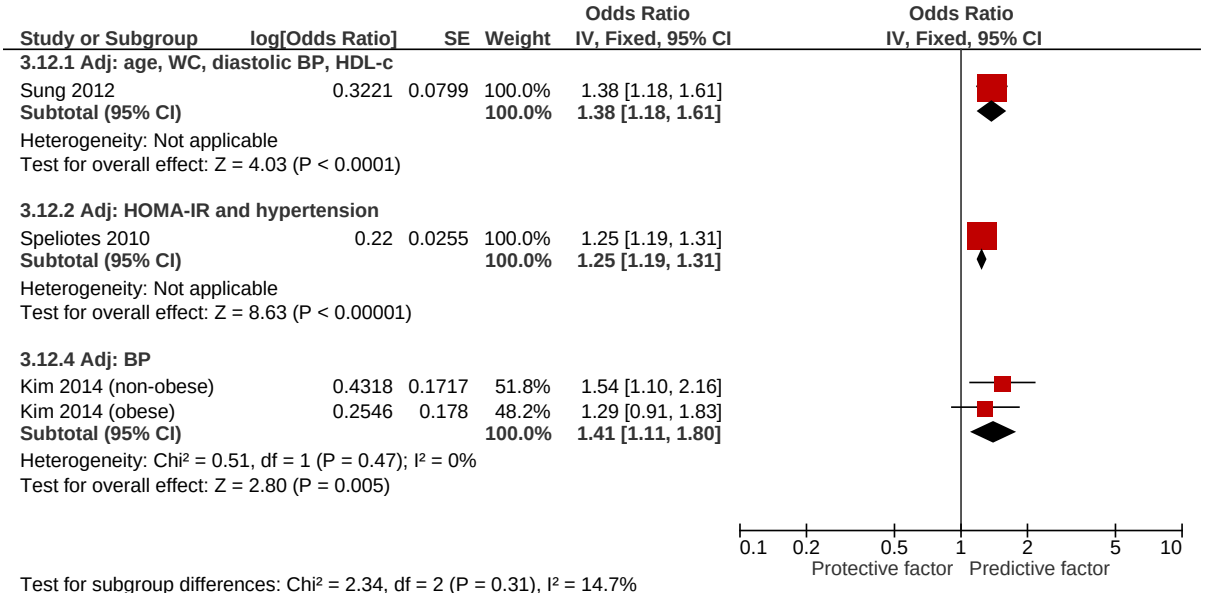


Triglycerides: Lee 2010- dichotomous factor (≥150 mg/dL), Xu 2013-dichotomous factor (no details)

2

3

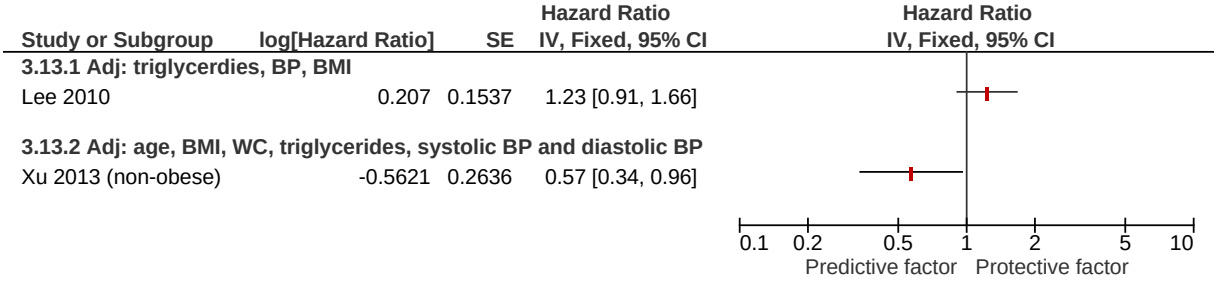
Figure 20: Triglycerides as a risk factor for NAFLD (Odds ratio) (adults



Triglycerides: Sung 2012: continuous factor, Speliotes 2010: dichotomous factor, Kim 2014: dichotomous factor (≥150 mg/dl)

1K.1.1.4 Low HDL-cholesterol

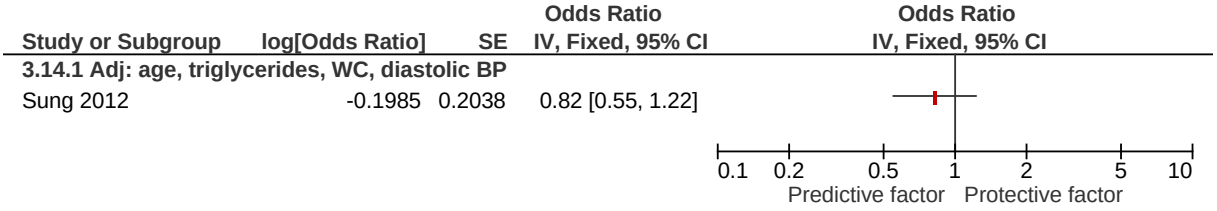
Figure 21: HDL-cholesterol as a prognostic risk factor for NAFLD (Hazard ratio) (adults)



HDL-cholesterol; Lee 2010: <40 (male) and <50 (female) mg/dL

2

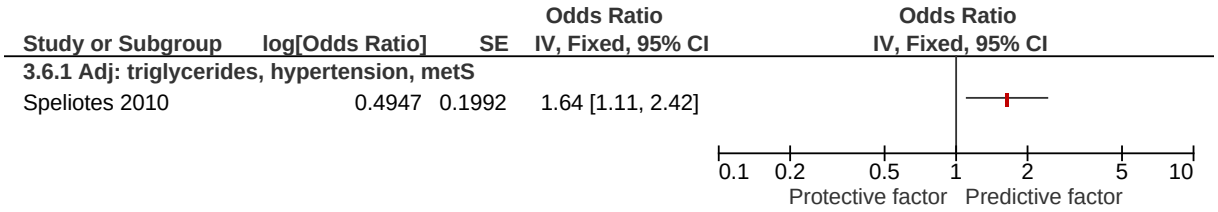
Figure 22: HDL-cholesterol as a prognostic risk factor for NAFLD (Odds ratio) (adults)



HDL-cholesterol: continuous factor

1**K.1.1.5** **Type 2 diabetes**

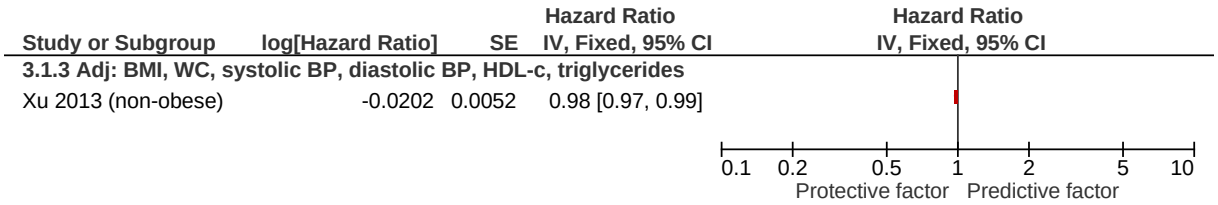
Figure 23: Type 2 diabetes as a prognostic risk factor for NAFLD (adults)



Diabetes-dichotomous factor (fasting plasma glucose of 126 mg/dL)

2**K.1.1.6** **Age**

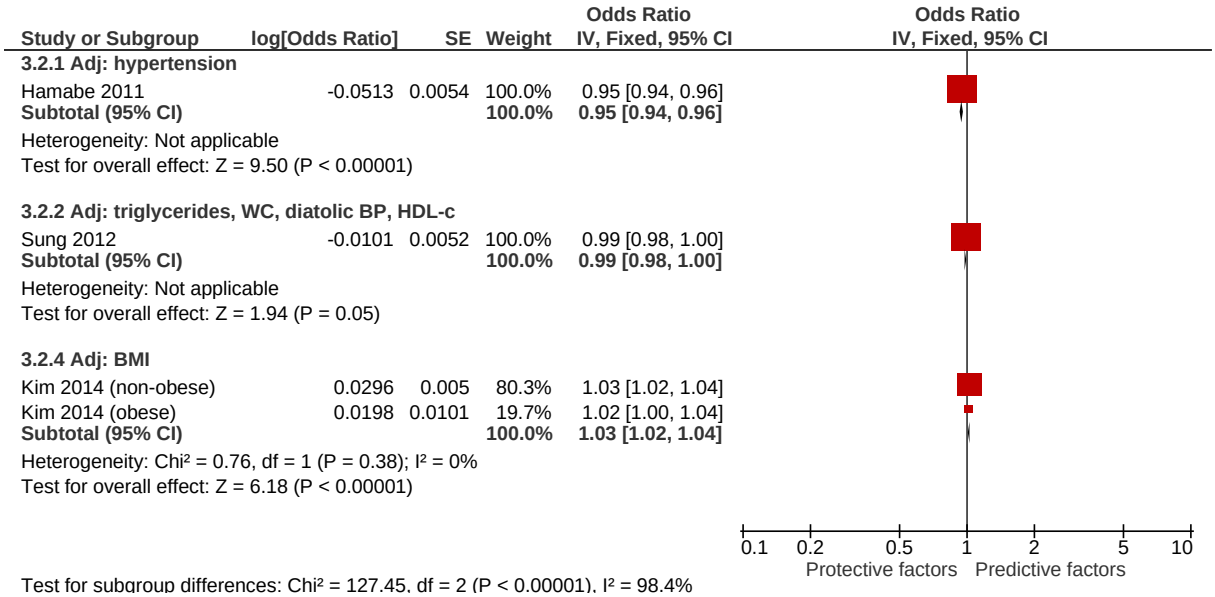
Figure 24: Age as a prognostic risk factor for NAFLD (Hazard ratios) (adults)



Age-dichotomous outcome (no details)

3

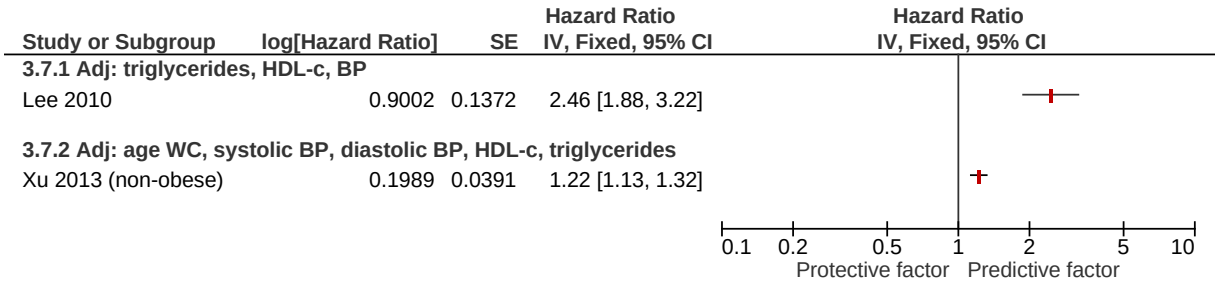
Figure 25: Age as a prognostic risk factor for NAFLD (Odds ratios)(adults)



Age; Hamabe2011- continuous factor, Sung 2012-continuous factor, Kim 2014- continuous factor

1K.1.1.7 BMI

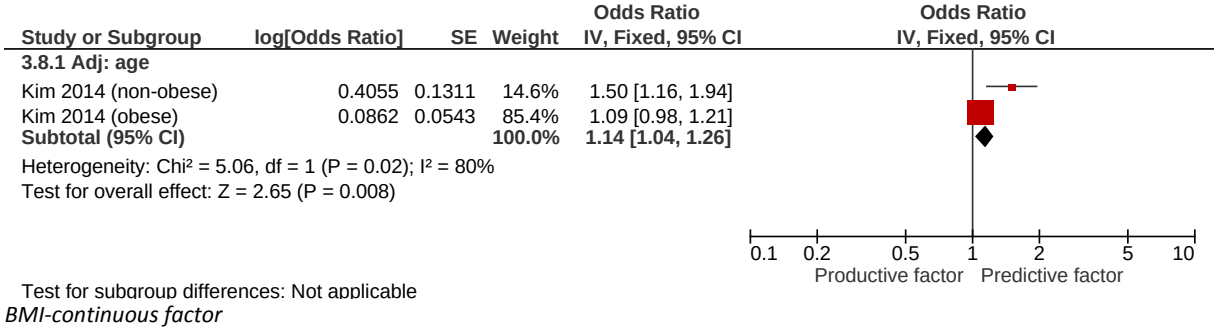
Figure 26: BMI as a prognostic risk factor for NAFLD (Hazard ratio) (adults)



BMI: Lee 2010: dichotomous factor (≥25 kg/m^2), Xu 2013: dichotomous (no details)

2

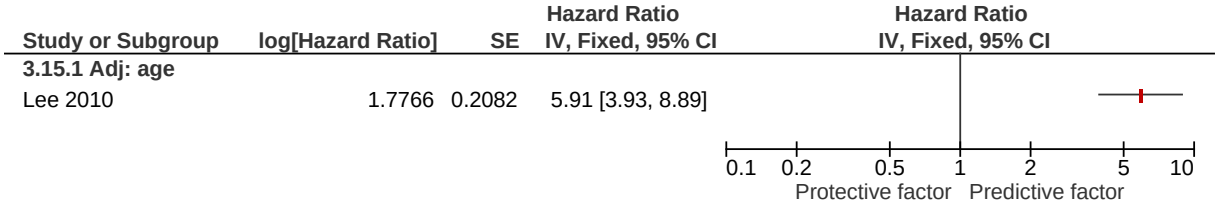
Figure 27: BMI as a prognostic risk factor for NAFLD (Odds ratio) (adults)



BMI-continuous factor

3K.1.1.8 Metabolic syndrome (combination of prognostic factors)

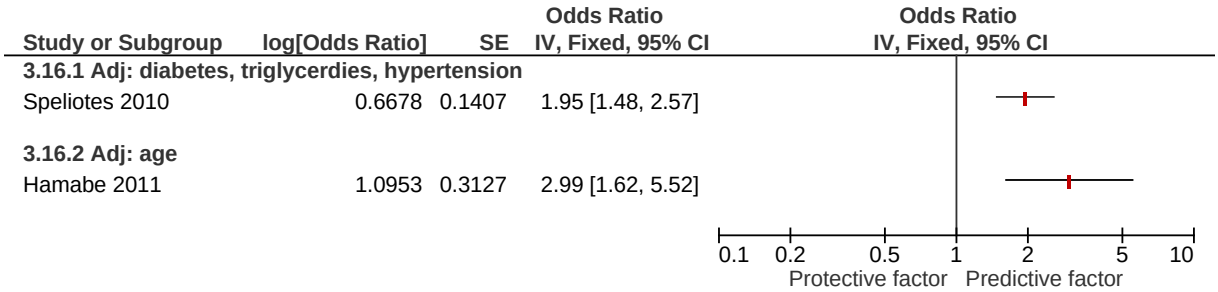
Figure 28: Metabolic syndrome as a prognostic risk factor for NAFLD (Hazard ratio) (adults)



Metabolic syndrome-dichotomous factor

4

Figure 29: Metabolic syndrome as a prognostic risk factor for NAFLD (Odds ratio) (adults)



Metabolic syndrome; Speliotes 2010: dichotomous facto, Hamabe 2011: dichotomous factor

1 K.2 Diagnosis of NAFLD

2 K.2.1 Diagnosing steatosis ≥5%

3K.2.1.1 Coupled sensitivity and specificity forest plots and pooled diagnostic meta-analysis plots

Figure 30: CAP for diagnosing steatosis ≥5%

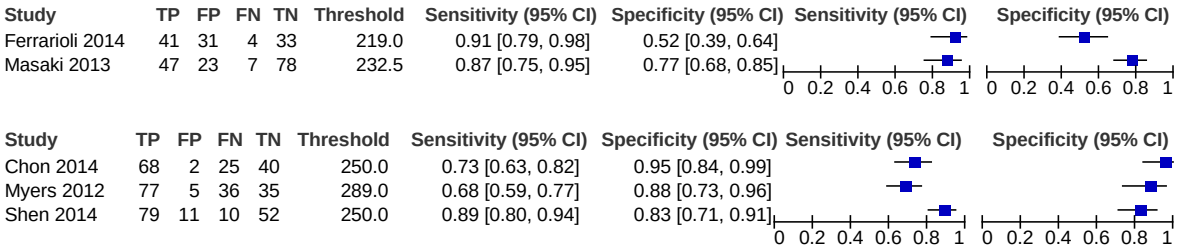


Figure 31: Diagnostic meta-analysis of CAP with a threshold range of 250-300 for diagnosing steatosis ≥5%

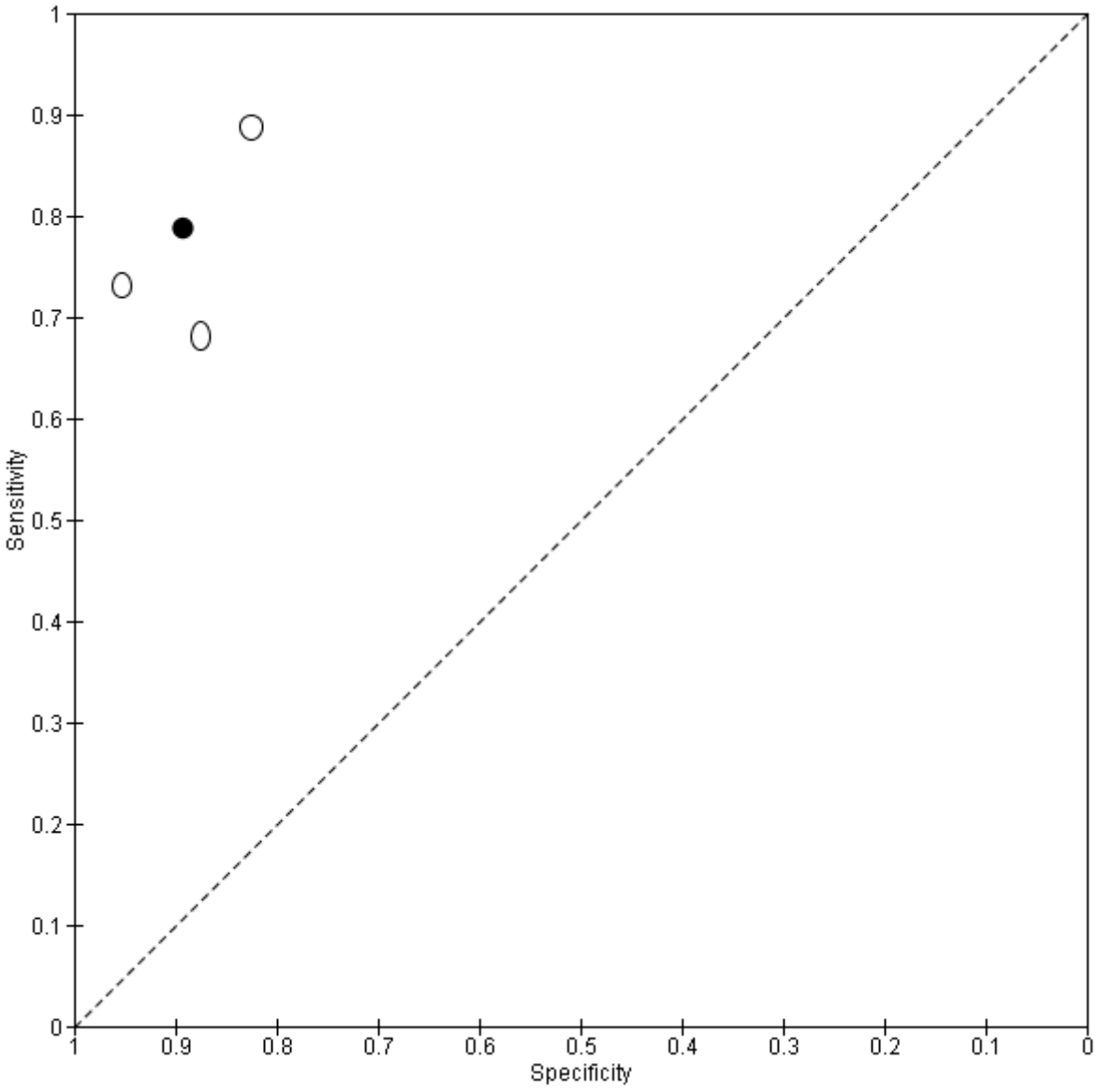


Figure 32: FLI for diagnosing steatosis ≥5%

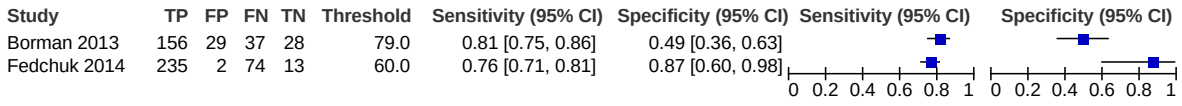
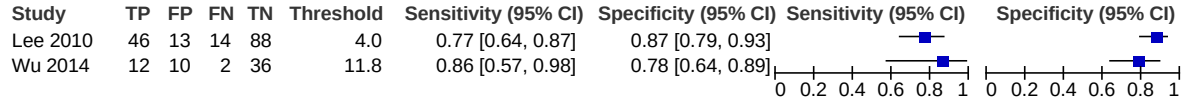
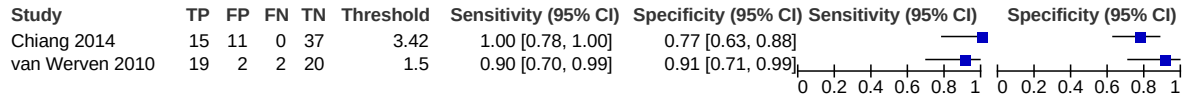


Figure 33: MRI-DE for diagnosing steatosis ≥5%



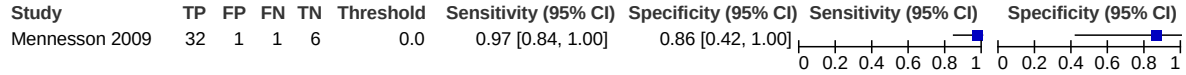
1

Figure 34: MRI fat-fraction for diagnosing steatosis ≥5%



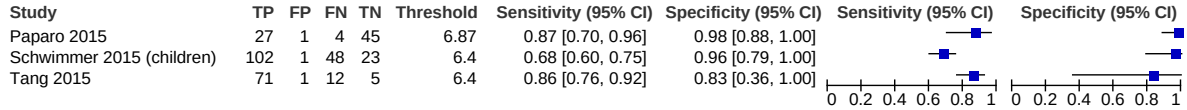
2

Figure 35: MRI fat-water ratio for diagnosing steatosis ≥5%



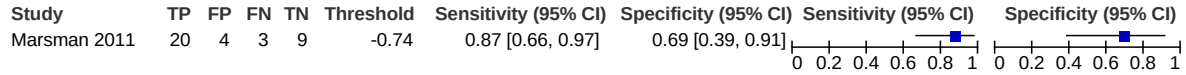
3

Figure 36: MRI PDFF for diagnosing steatosis ≥5%



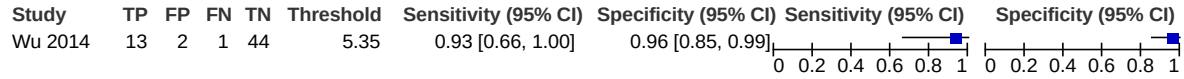
4

Figure 37: MRI %RSID for diagnosing steatosis ≥5%



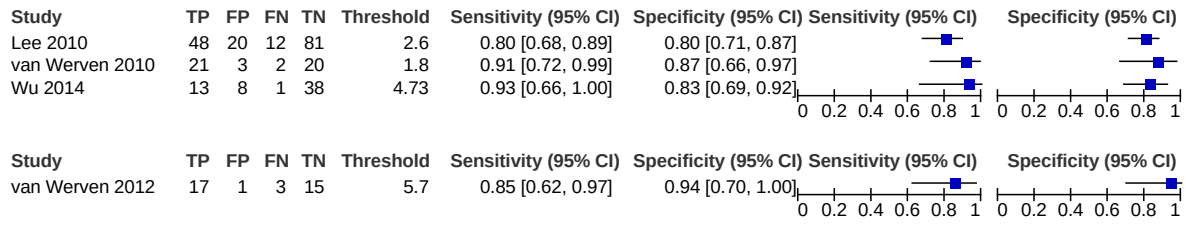
5

Figure 38: MRI-TE for diagnosing steatosis ≥5%



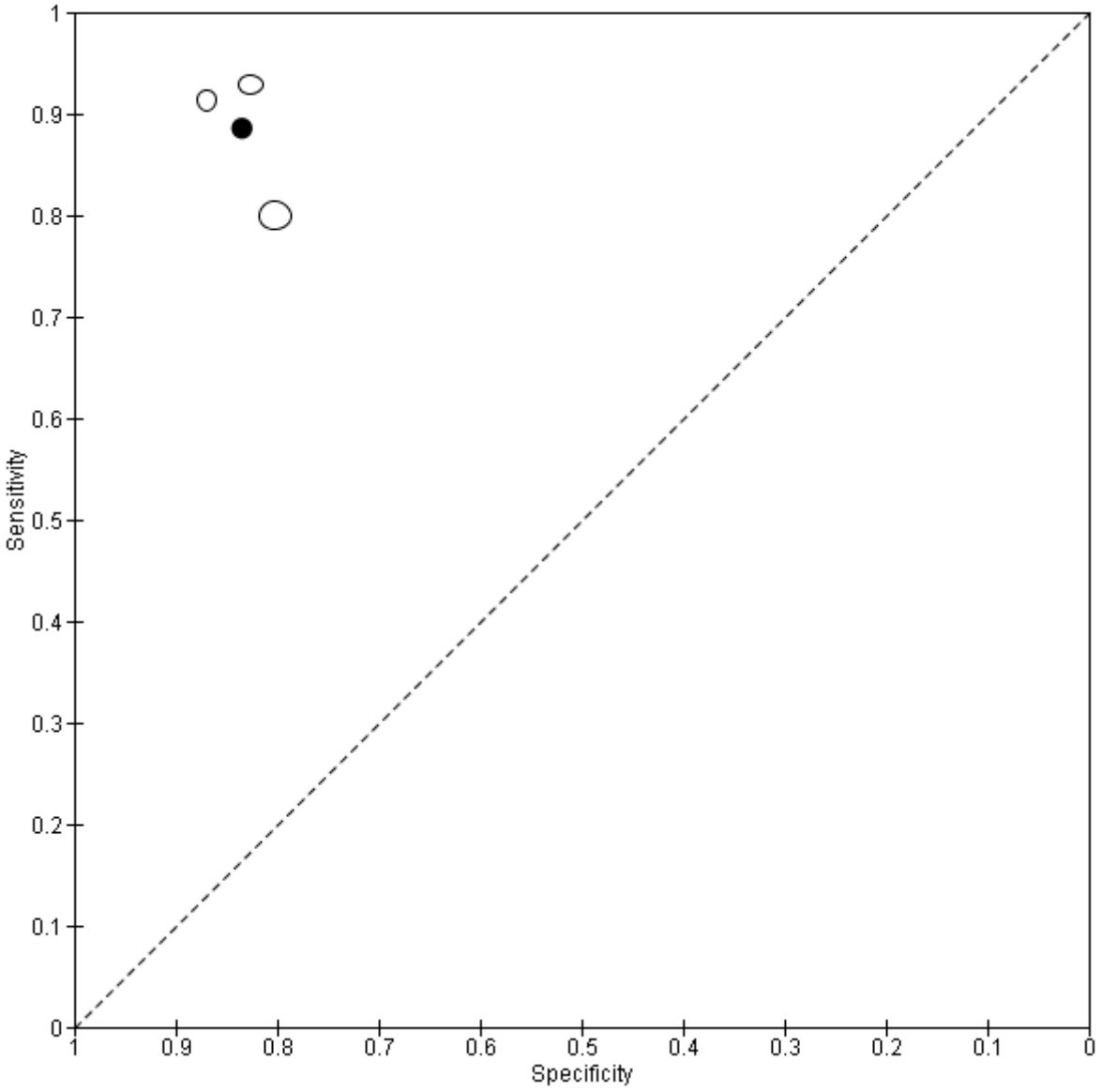
6

Figure 39: MRS for diagnosing steatosis ≥5%



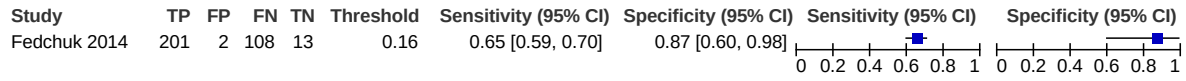
7

Figure 40: Diagnostic meta-analysis of MRS with a threshold range of 0-5 for diagnosing steatosis ≥5%



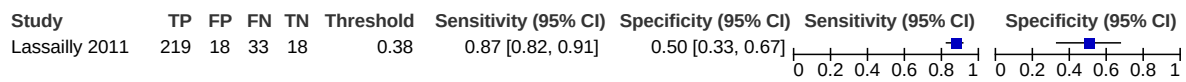
1

Figure 41: NAFLD-LFS for diagnosing steatosis ≥5%



2

Figure 42: Steatotest for diagnosing steatosis ≥5%



3

Figure 43: Ultrasound (no threshold specified) for diagnosing steatosis ≥5%

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Dasarathy 2009	38	0	8	27		0.83 [0.69, 0.92]	1.00 [0.87, 1.00]
de Moura Almeida 2008	61	1	33	10		0.65 [0.54, 0.74]	0.91 [0.59, 1.00]
Jun 2014	903	262	858	1833		0.51 [0.49, 0.54]	0.87 [0.86, 0.89]
Lee 2007	151	25	152	261		0.50 [0.44, 0.56]	0.91 [0.87, 0.94]
van Werven 2010	13	5	7	17		0.65 [0.41, 0.85]	0.77 [0.55, 0.92]
Wang 2014	43	27	17	84		0.72 [0.59, 0.83]	0.76 [0.67, 0.83]

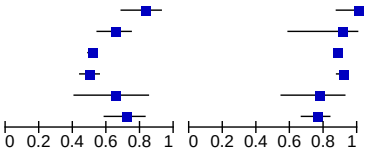


Figure 44: Diagnostic meta-analysis of ultrasound for diagnosing steatosis ≥5%

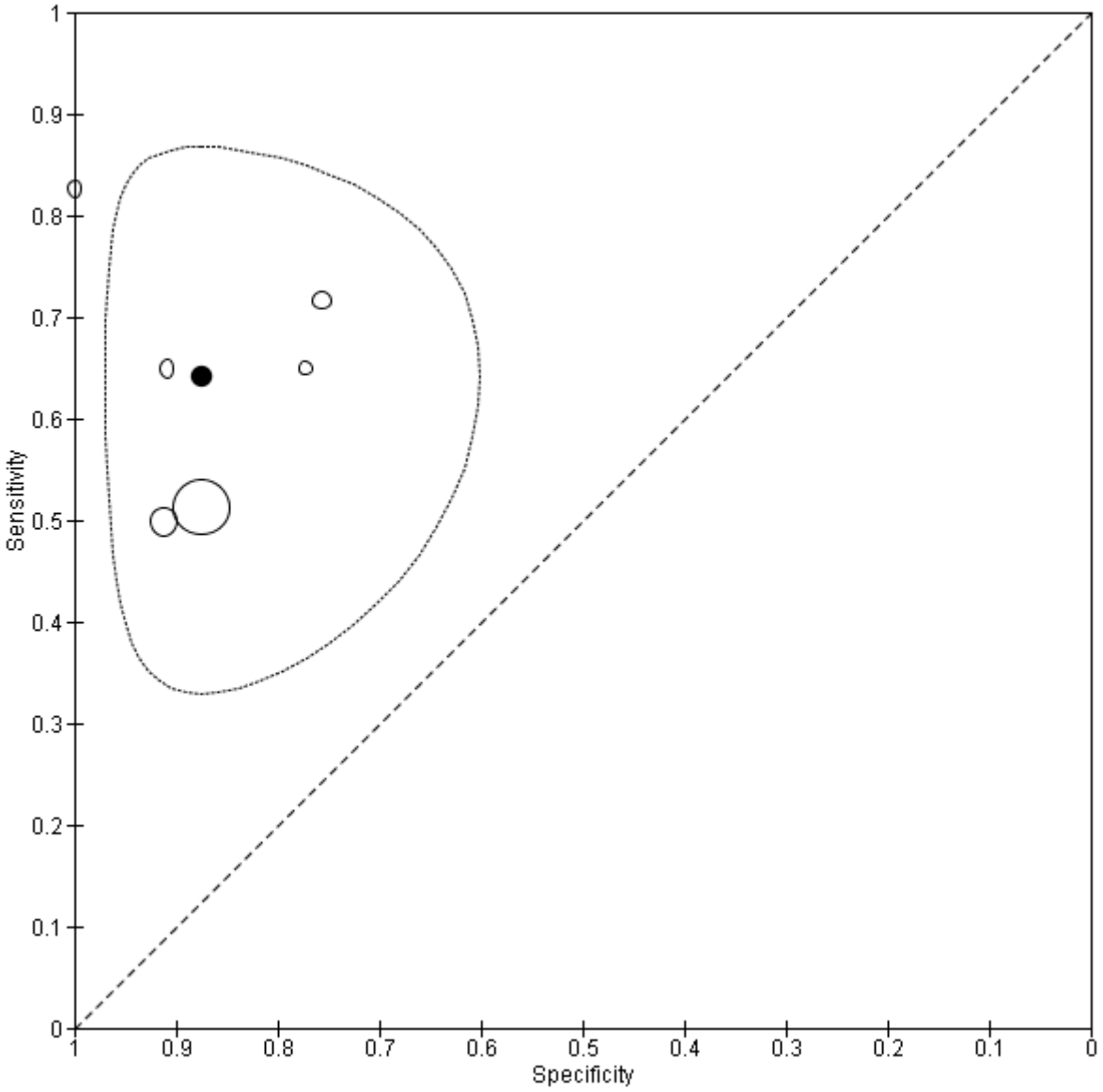
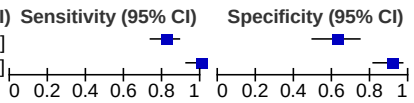


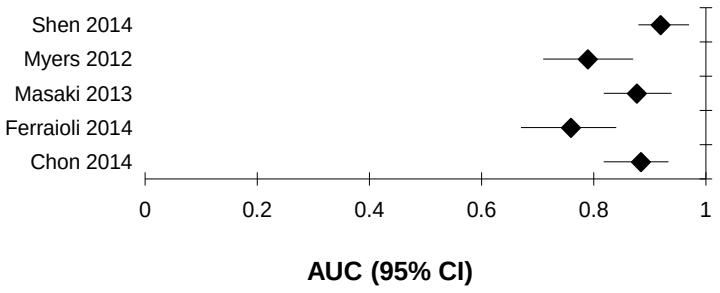
Figure 45: Ultrasound (hepatorenal contrast) for diagnosing steatosis ≥5%

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Wang 2013	91	24	20	40	4.0	0.82 [0.74, 0.89]	0.63 [0.50, 0.74]
Webb 2009	45	6	0	60	1.49	1.00 [0.92, 1.00]	0.91 [0.81, 0.97]



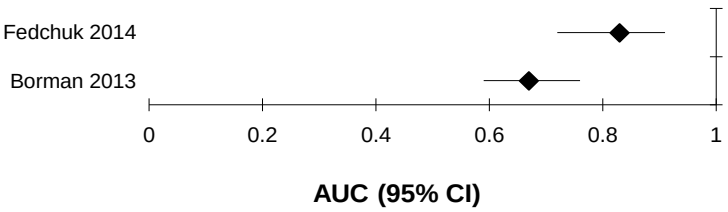
1K.2.1.2 Area under the curve plot

Figure 46: CAP steatosis ≥5%



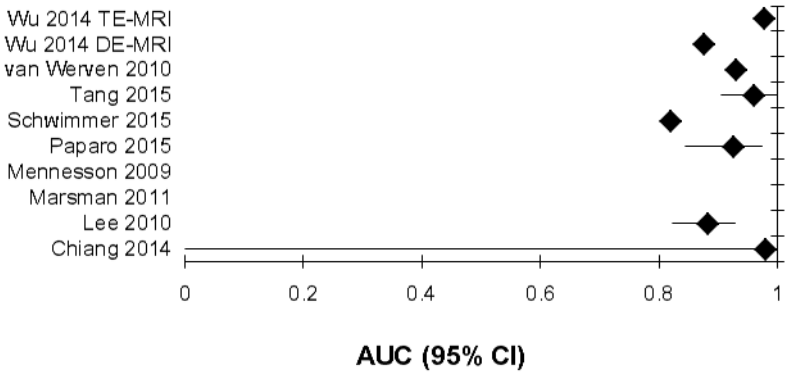
2

Figure 47: FLI steatosis ≥5%



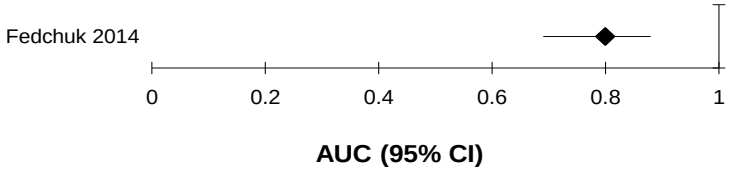
3

Figure 48: MRI steatosis ≥5%



4

Figure 49: MRS steatosis ≥5%

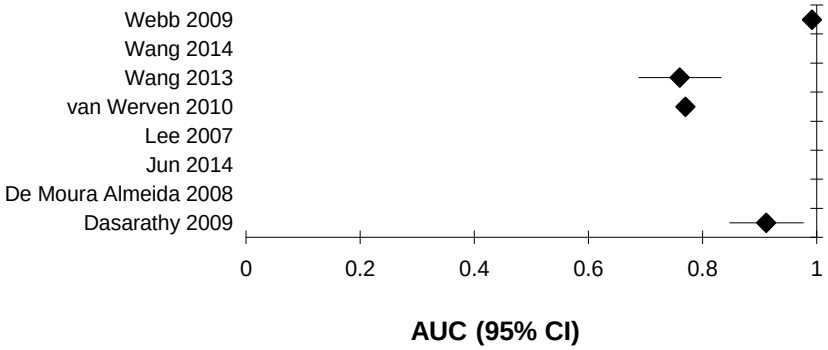


5

Figure 50: Steatotest steatosis ≥5%

None reported

Figure 51: Ultrasound steatosis ≥5%



K.2.2 Diagnosing steatosis ≥30%

K.2.2.1 Coupled sensitivity and specificity forest plots and pooled diagnostic meta-analysis plots

Figure 52: CAP for diagnosing steatosis ≥30%

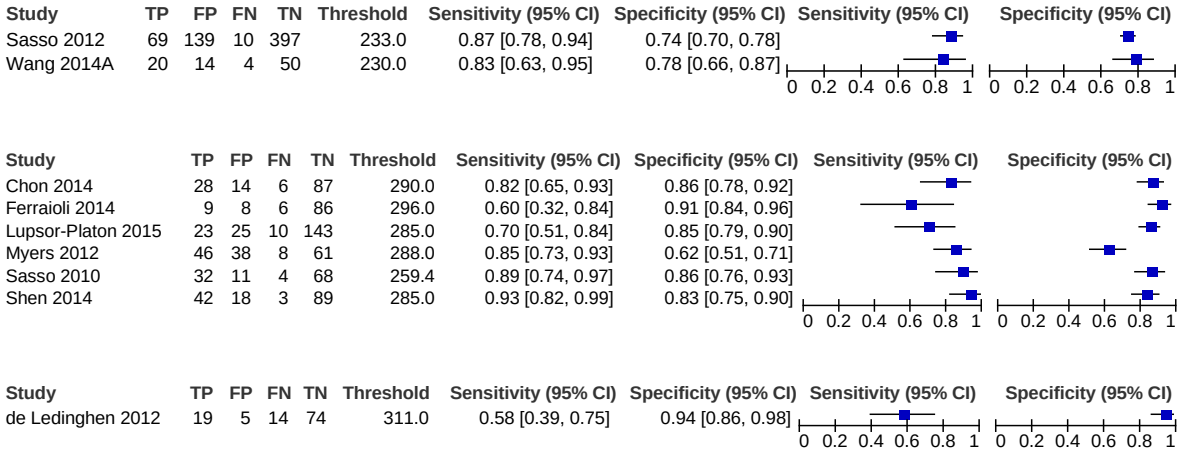
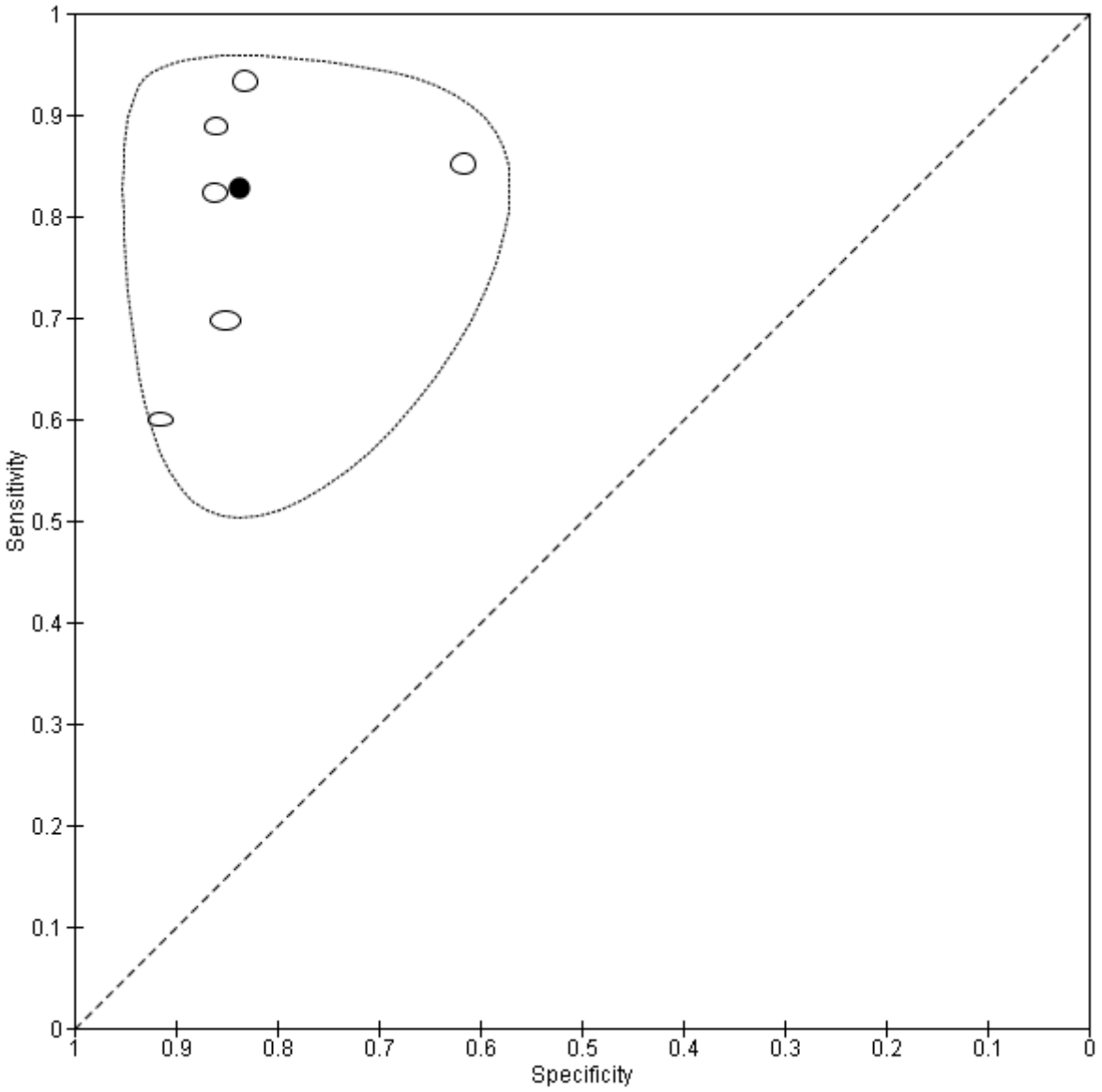
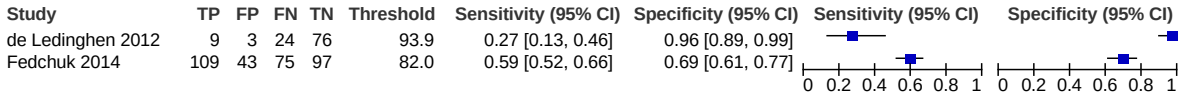


Figure 53: Diagnostic meta-analysis of CAP with threshold range of 250-300 for diagnosing steatosis ≥30%



1

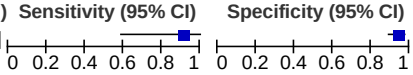
Figure 54: FLI for diagnosing steatosis ≥30%



2

Figure 55: MRI-DE for diagnosing steatosis ≥30%

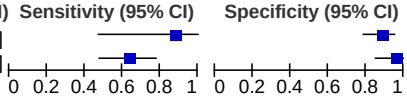
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Lee 2010	10	9	1	141	6.5	0.91 [0.59, 1.00]	0.94 [0.89, 0.97]



1

Figure 56: MRI-PDFF for diagnosing steatosis ≥30%

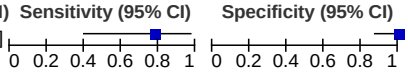
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Paparo 2015	7	8	1	61	11.08	0.88 [0.47, 1.00]	0.88 [0.78, 0.95]
Tang 2015	28	2	16	43	22.1	0.64 [0.48, 0.78]	0.96 [0.85, 0.99]



2

Figure 57: MRI %RSID for diagnosing steatosis ≥30%

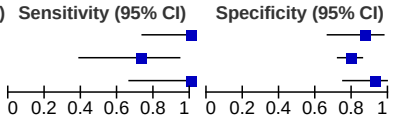
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Marsman 2011	7	0	2	27	19.22	0.78 [0.40, 0.97]	1.00 [0.87, 1.00]



3

Figure 58: MRS for diagnosing steatosis ≥30%

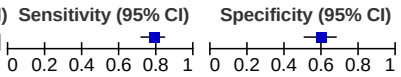
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Koelblinger 2012	12	3	0	20	2.7	1.00 [0.74, 1.00]	0.87 [0.66, 0.97]
Lee 2010	8	31	3	119	7.7	0.73 [0.39, 0.94]	0.79 [0.72, 0.86]
Urdzik 2012	9	2	0	24	10.2	1.00 [0.66, 1.00]	0.92 [0.75, 0.99]



4

Figure 59: NAFLD LFS for diagnosing steatosis ≥30%

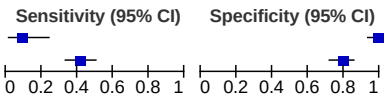
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Fedchuk 2014	144	57	40	83	0.16	0.78 [0.72, 0.84]	0.59 [0.51, 0.68]



5

Figure 60: Steatotest for diagnosing steatosis ≥30%

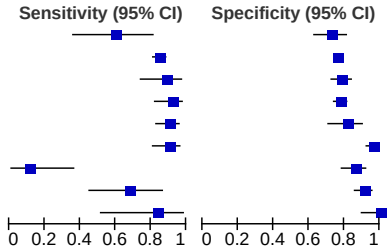
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
de Ledinghen 2012	3	1	30	78	0.94	0.09 [0.02, 0.24]	0.99 [0.93, 1.00]
Lassailly 2011	58	31	81	118	0.69	0.42 [0.33, 0.50]	0.79 [0.72, 0.85]



6

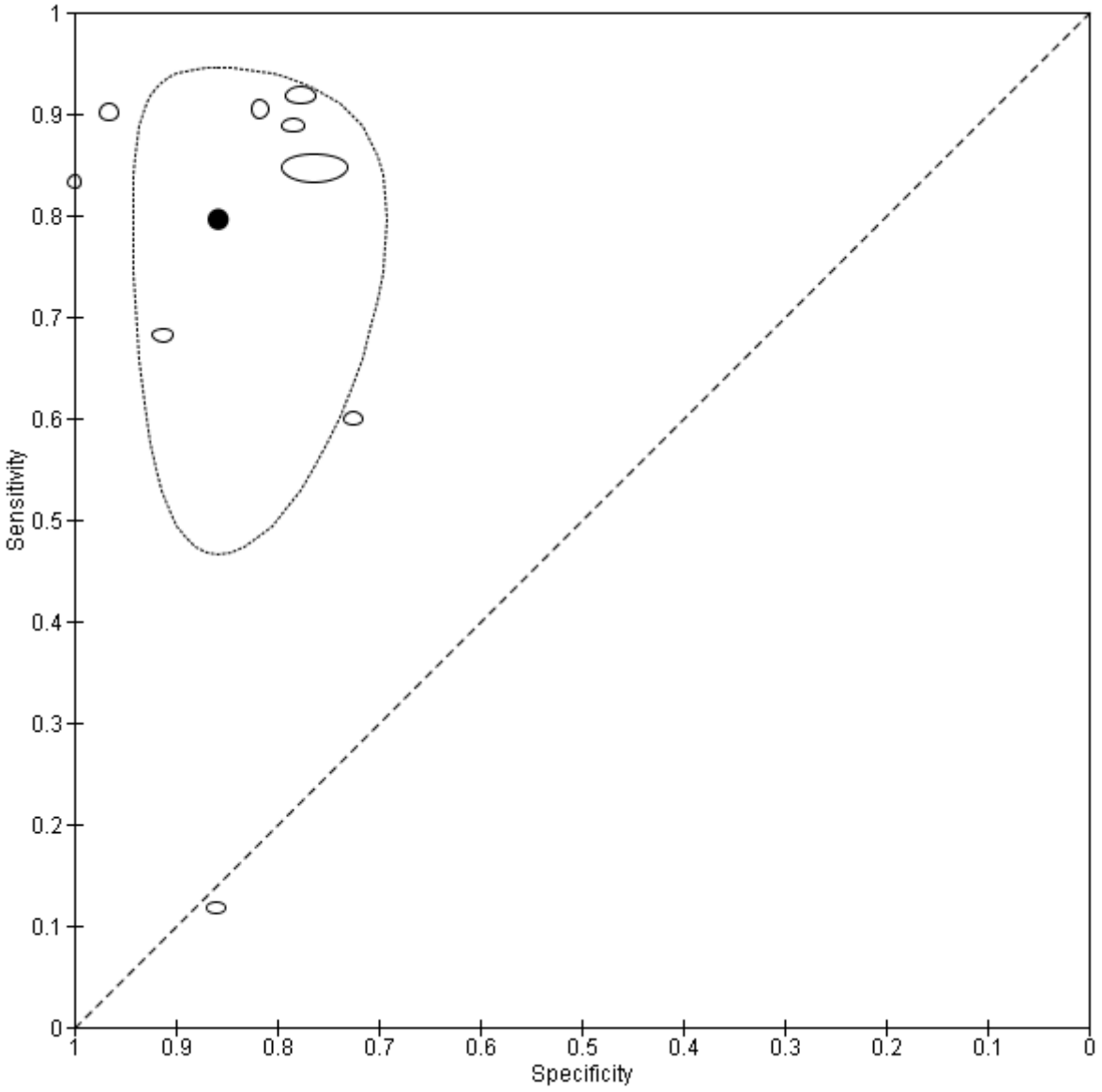
Figure 61: Ultrasound (no threshold specified) for diagnosing steatosis ≥30%

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Hepburn 2005	12	28	8	74		0.60 [0.36, 0.81]	0.73 [0.63, 0.81]
Jun 2014	343	818	62	2633		0.85 [0.81, 0.88]	0.76 [0.75, 0.78]
Junior 2012	32	48	4	175		0.89 [0.74, 0.97]	0.78 [0.72, 0.84]
Lee 2007	56	118	5	410		0.92 [0.82, 0.97]	0.78 [0.74, 0.81]
Mathiesen 2002	85	13	9	58		0.90 [0.83, 0.96]	0.82 [0.71, 0.90]
Palmentieri 2006	64	5	7	140		0.90 [0.81, 0.96]	0.97 [0.92, 0.99]
Perez 2007	2	16	15	98		0.12 [0.01, 0.36]	0.86 [0.78, 0.92]
Wang 2014	15	13	7	136		0.68 [0.45, 0.86]	0.91 [0.86, 0.95]
Yajima 1983	10	0	2	33		0.83 [0.52, 0.98]	1.00 [0.89, 1.00]



1

Figure 62: Diagnostic meta-analysis of ultrasound for diagnosing steatosis ≥30%



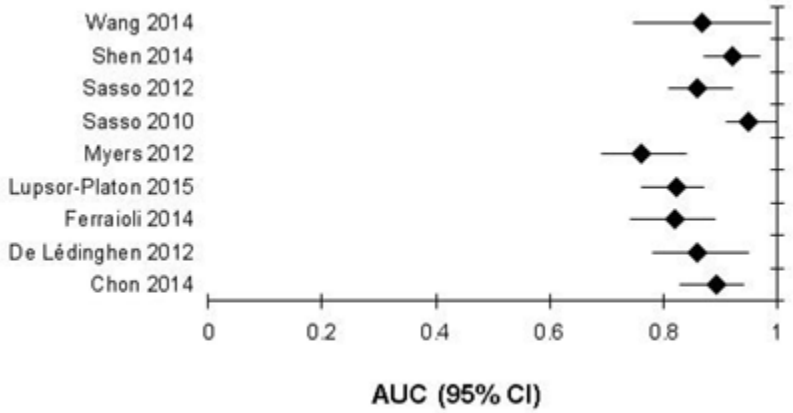
2

Figure 63: Ultrasound (hepatorenal contrast) for diagnosing steatosis ≥30

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wang 2013	24	22	4	125	7.0	0.86 [0.67, 0.96]	0.85 [0.78, 0.90]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

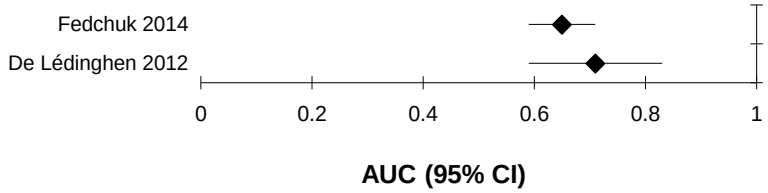
1K.2.2.2 Area under the curve plot

Figure 64: CAP steatosis ≥30%



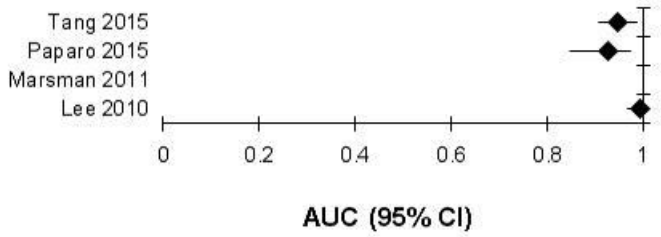
2

Figure 65: FLI steatosis ≥30%



3

Figure 66: MRI steatosis ≥30%



4

Figure 67: MRS steatosis ≥30%

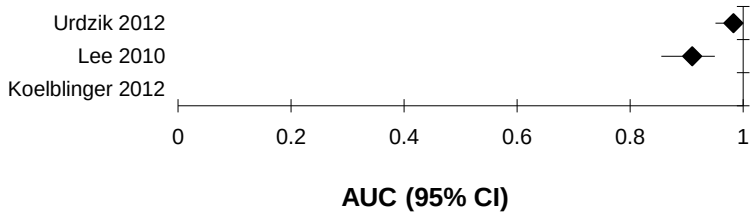


Figure 68: NAFLD-LFS steatosis ≥30%

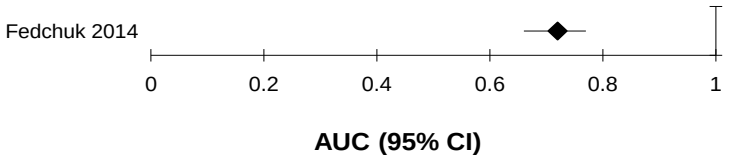


Figure 69: Steatotest steatosis ≥30%

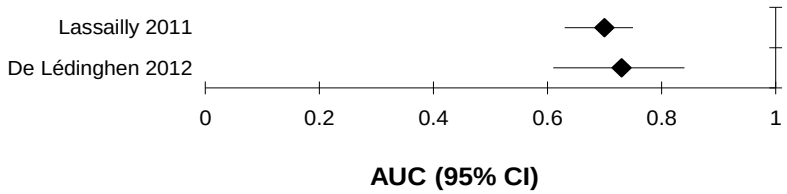
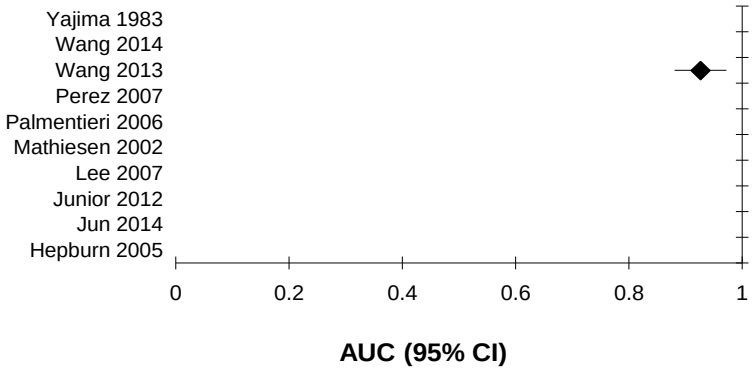


Figure 70: Ultrasound steatosis ≥30%

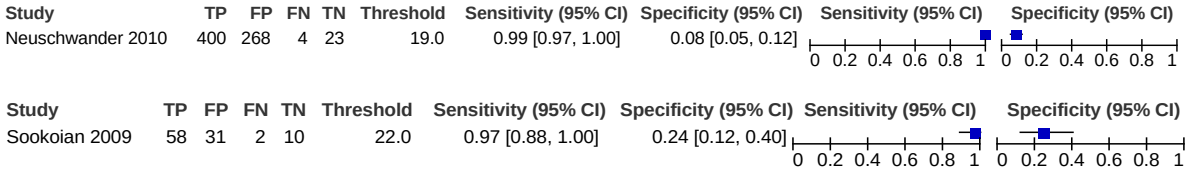


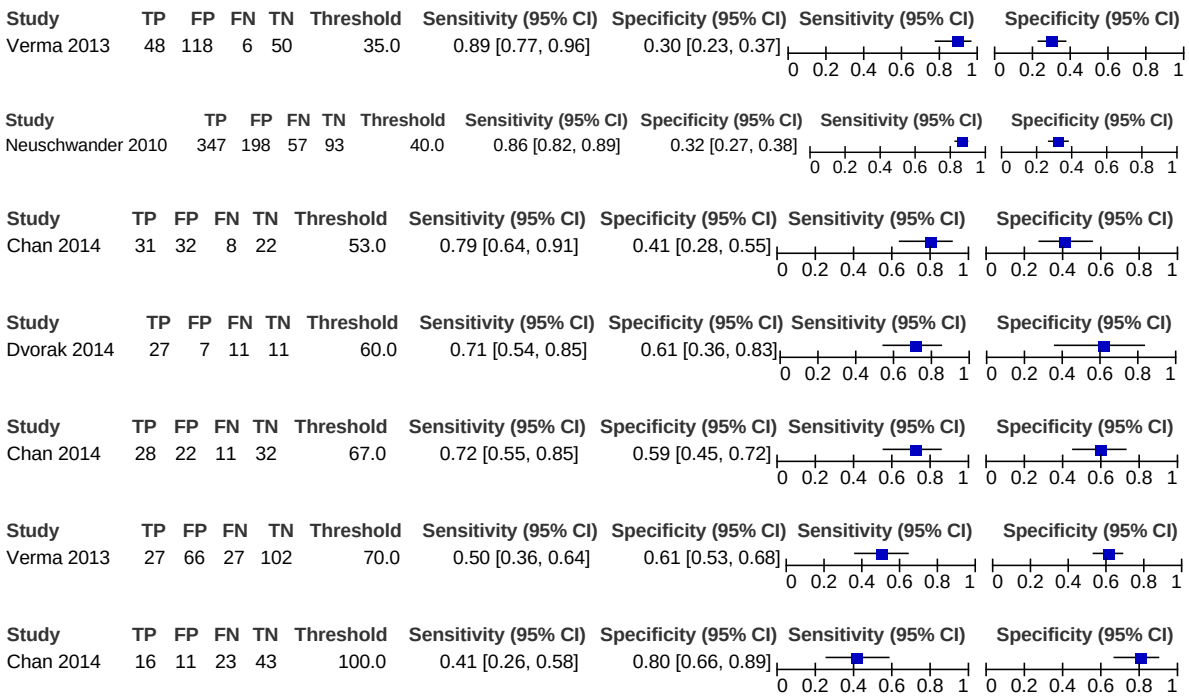
K.3 Diagnosing the severity of NAFLD

K.3.1 Diagnosing NASH

K.3.1.1 Coupled sensitivity and specificity forest plots

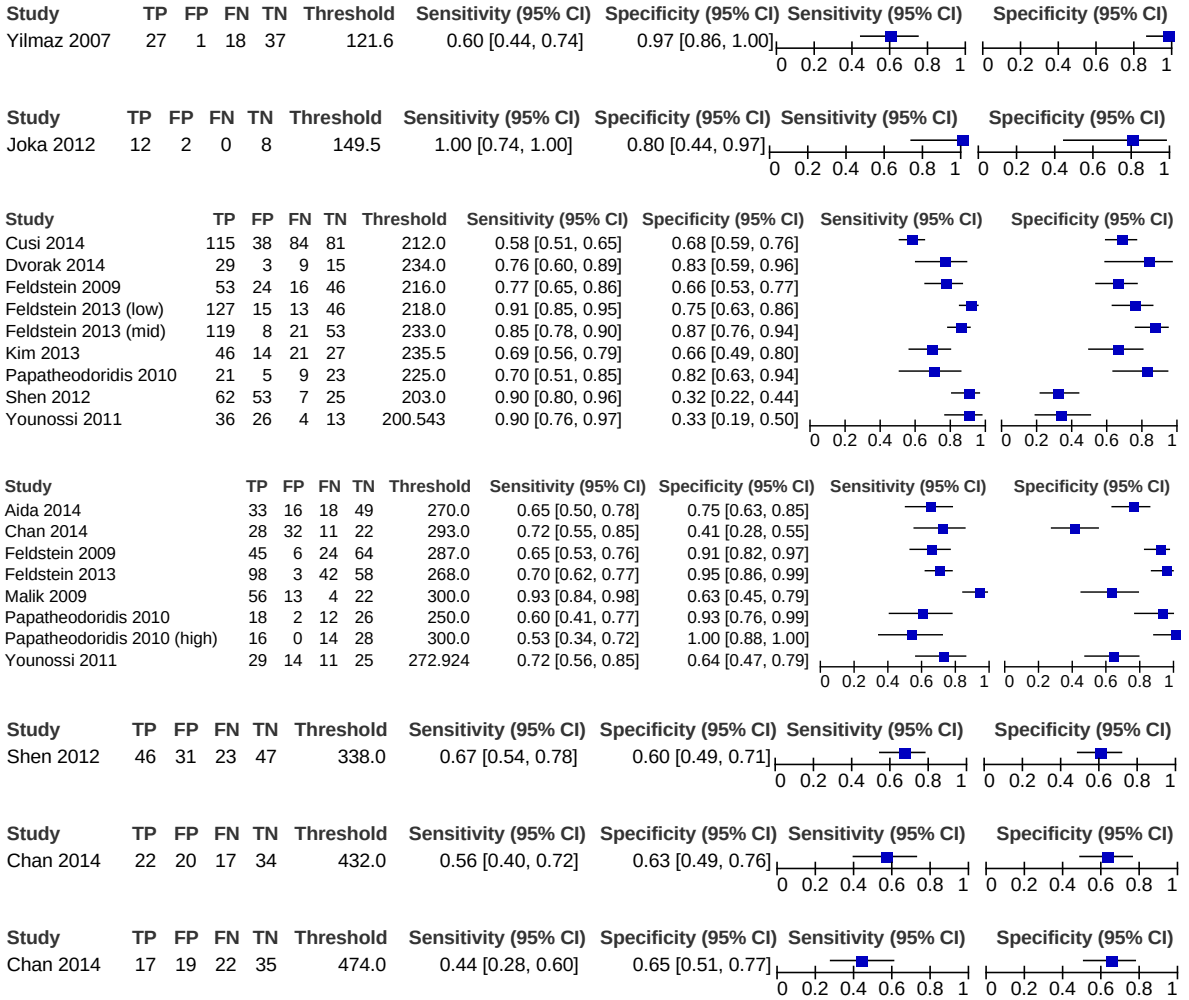
Figure 71: ALT levels for diagnosing NASH at increasing thresholds from 19 to 100

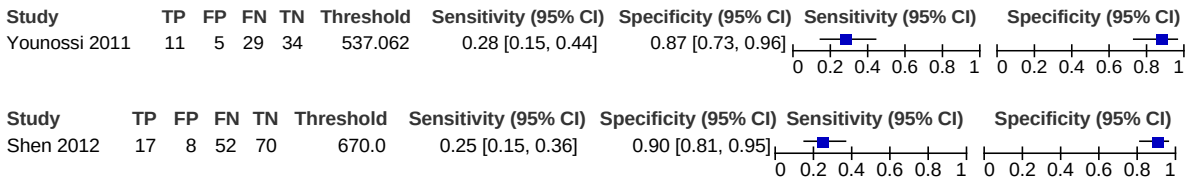




1

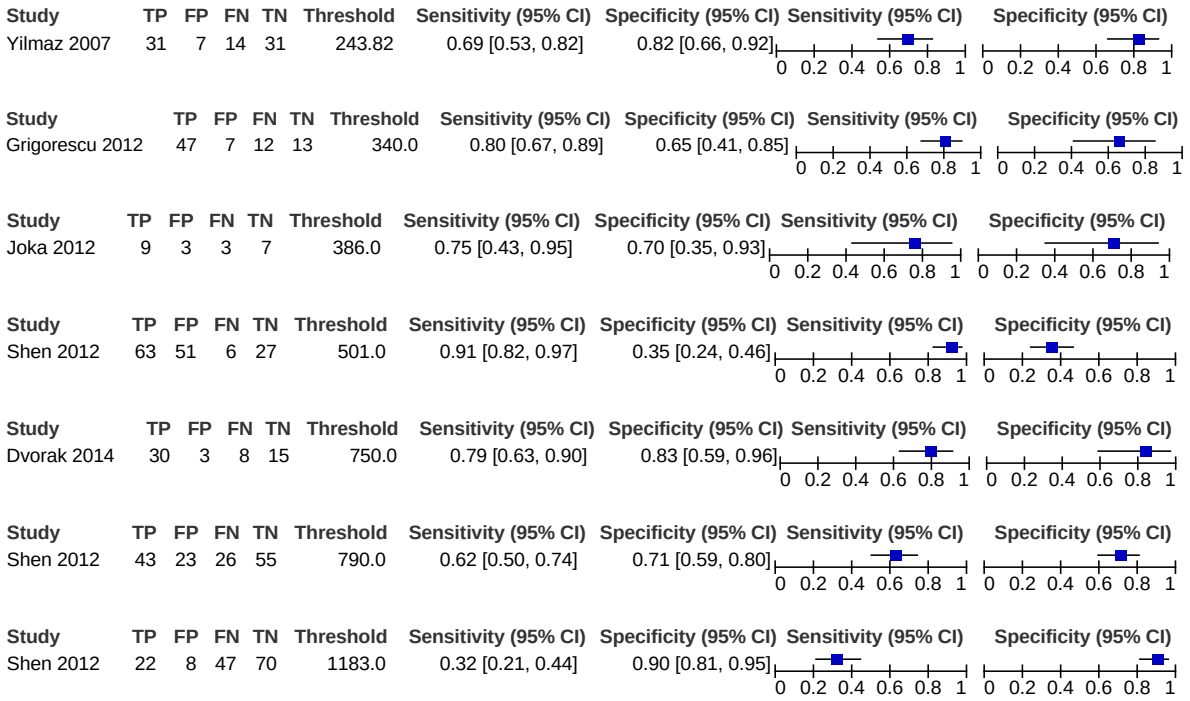
Figure 72: CK 18 [M30] for diagnosing NASH at increasing thresholds from 121.6 to 670





1

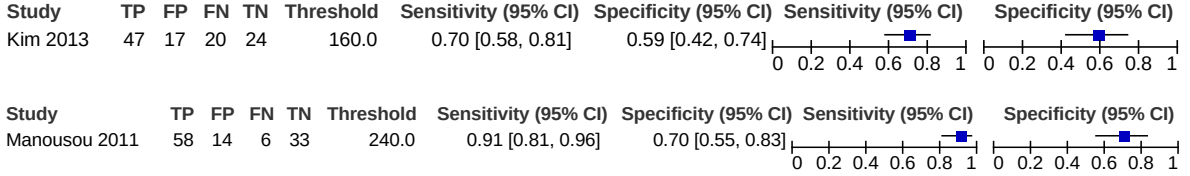
Figure 73: CK 18 [M65] for diagnosing NASH at increasing thresholds from 242.82 to 1183



2

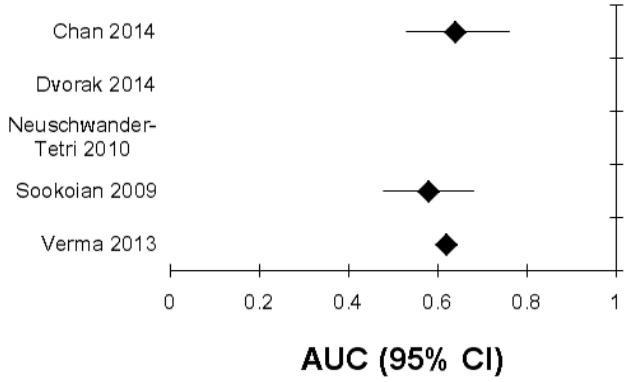
3

Figure 74: Ferritin for diagnosing NASH at increasing thresholds from 160 to 240



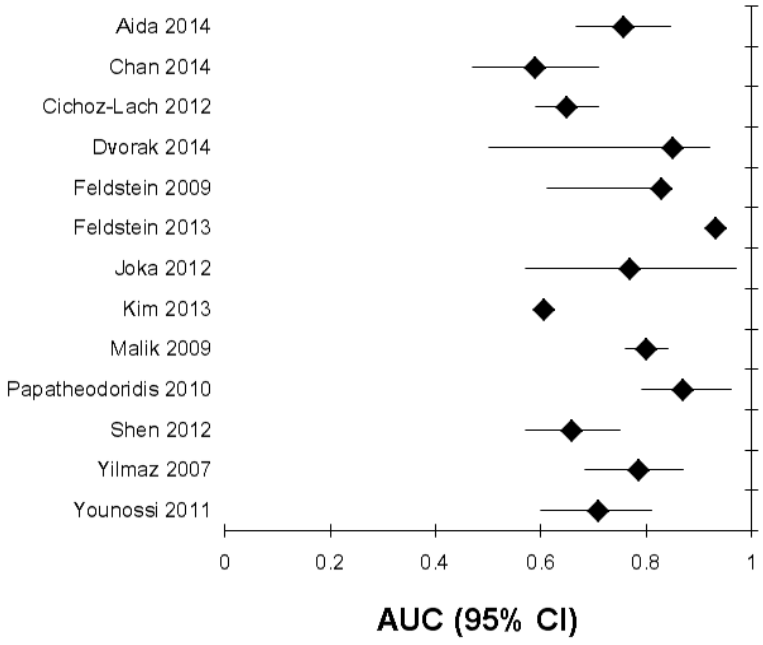
1K.3.1.2 Area under the curve plots

Figure 75: ALT for NASH



2

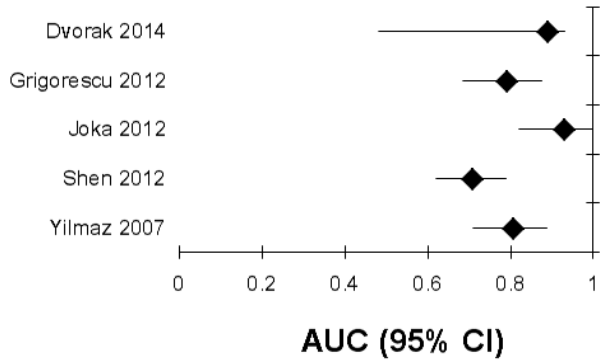
Figure 76: CK 18 [M30] for NASH



3

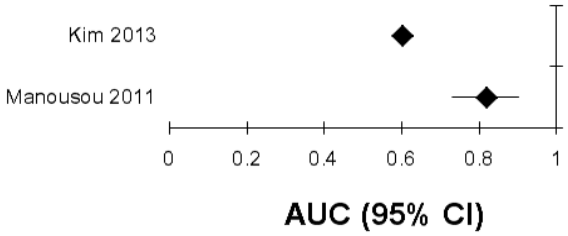
4

Figure 77: CK 18 [M65] for NASH



1

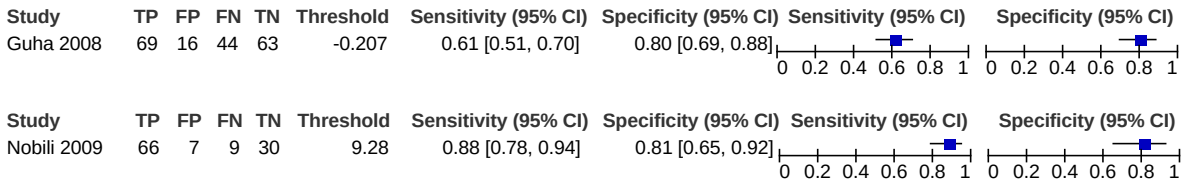
Figure 78: Ferritin for NASH



2 K.3.2 Diagnosing any fibrosis (≥F1)

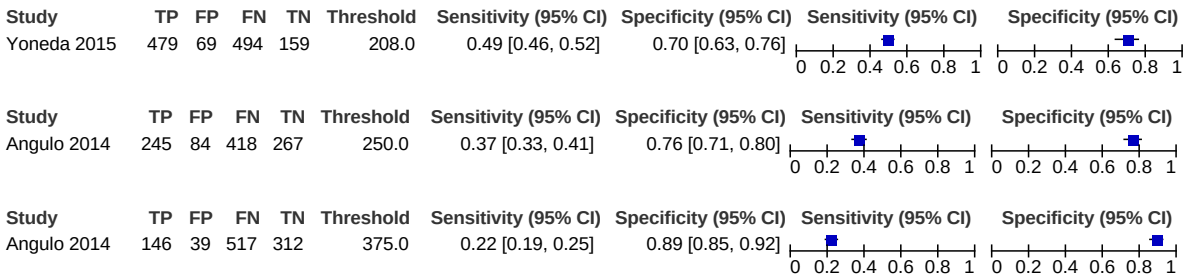
3K.3.2.1 Coupled sensitivity and specificity forest plots

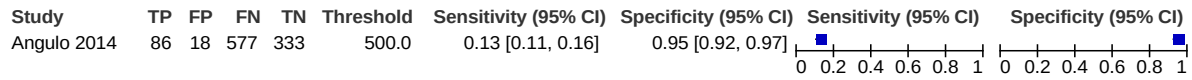
Figure 79: Enhanced Liver Fibrosis (ELF) score for diagnosing any fibrosis at increasing thresholds from -0.207 to 9.28



4

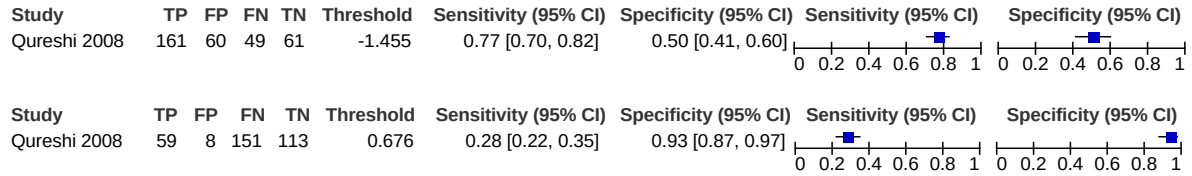
Figure 80: Ferritin for diagnosing any fibrosis at increasing thresholds from 208 to 500





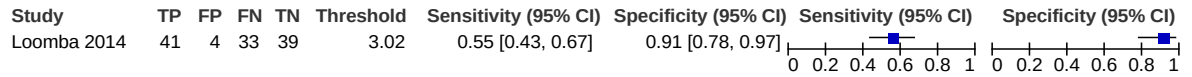
1

Figure 81: NAFLD fibrosis score for diagnosing any fibrosis at increasing thresholds from -1.455 to 0.676



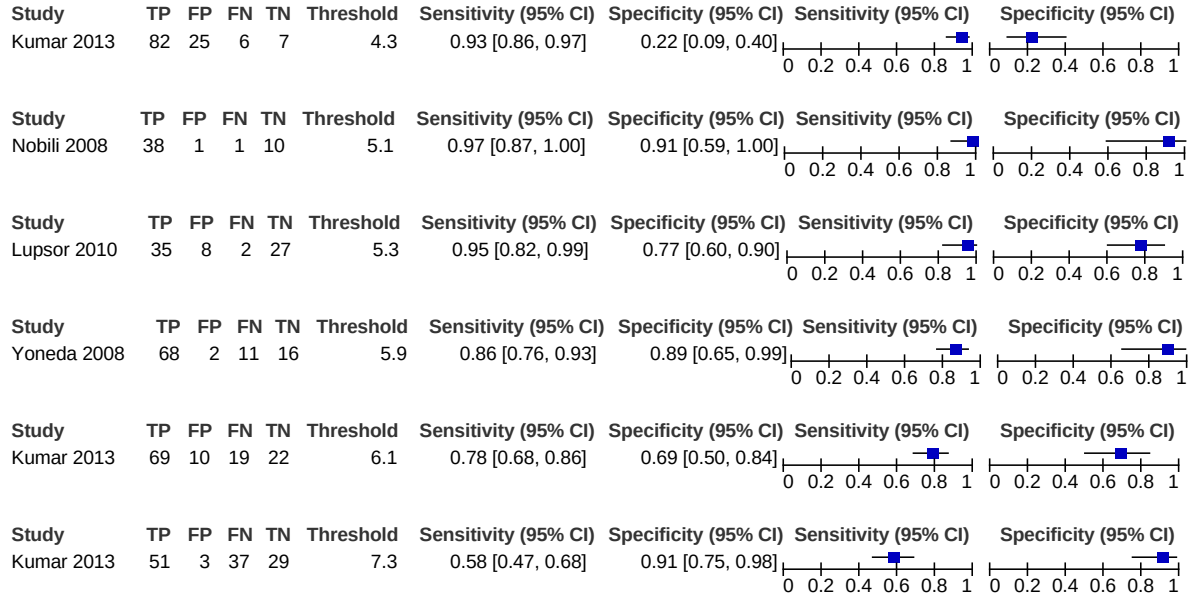
2

Figure 82: MR elastography for diagnosing any fibrosis



3

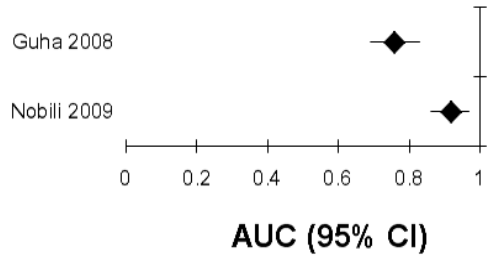
Figure 83: Transient elastography for diagnosing any fibrosis at increasing thresholds from 4.3 to 7.3



4

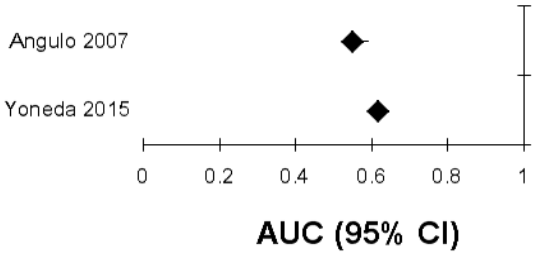
1K.3.2.2 Area under the curve plots

Figure 84: ELF any fibrosis



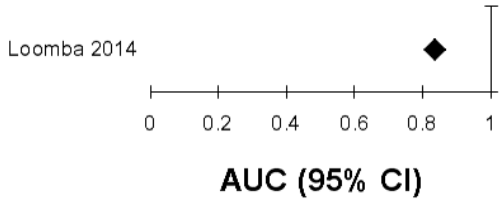
2

Figure 85: Ferritin any fibrosis



3

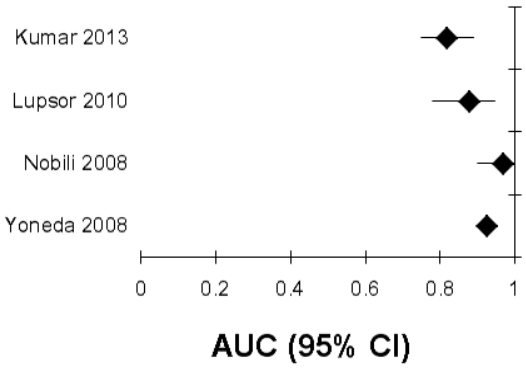
Figure 86: MRE any fibrosis



4

5

Figure 87: TE any fibrosis

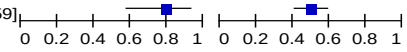


1 K.3.3 Diagnosing advanced fibrosis

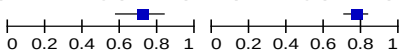
2K.3.3.1 Coupled sensitivity and specificity forest plots and pooled diagnostic meta-analysis plots

Figure 88: APRI for diagnosing advanced fibrosis at increasing thresholds from 0.5 to 1

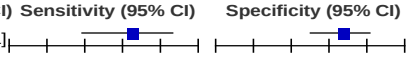
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Mahadeva 2013	15	18	14	84	0.5	0.52 [0.33, 0.71]	0.82 [0.74, 0.89]		
Xun 2012	19	64	5	64	0.5	0.79 [0.58, 0.93]	0.50 [0.41, 0.59]		



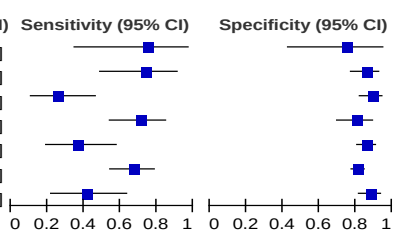
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Adams 2011	38	43	15	146	0.54	0.72 [0.58, 0.83]	0.77 [0.71, 0.83]		



Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dvorak 2014	11	13	6	26	0.65	0.65 [0.38, 0.86]	0.67 [0.50, 0.81]		

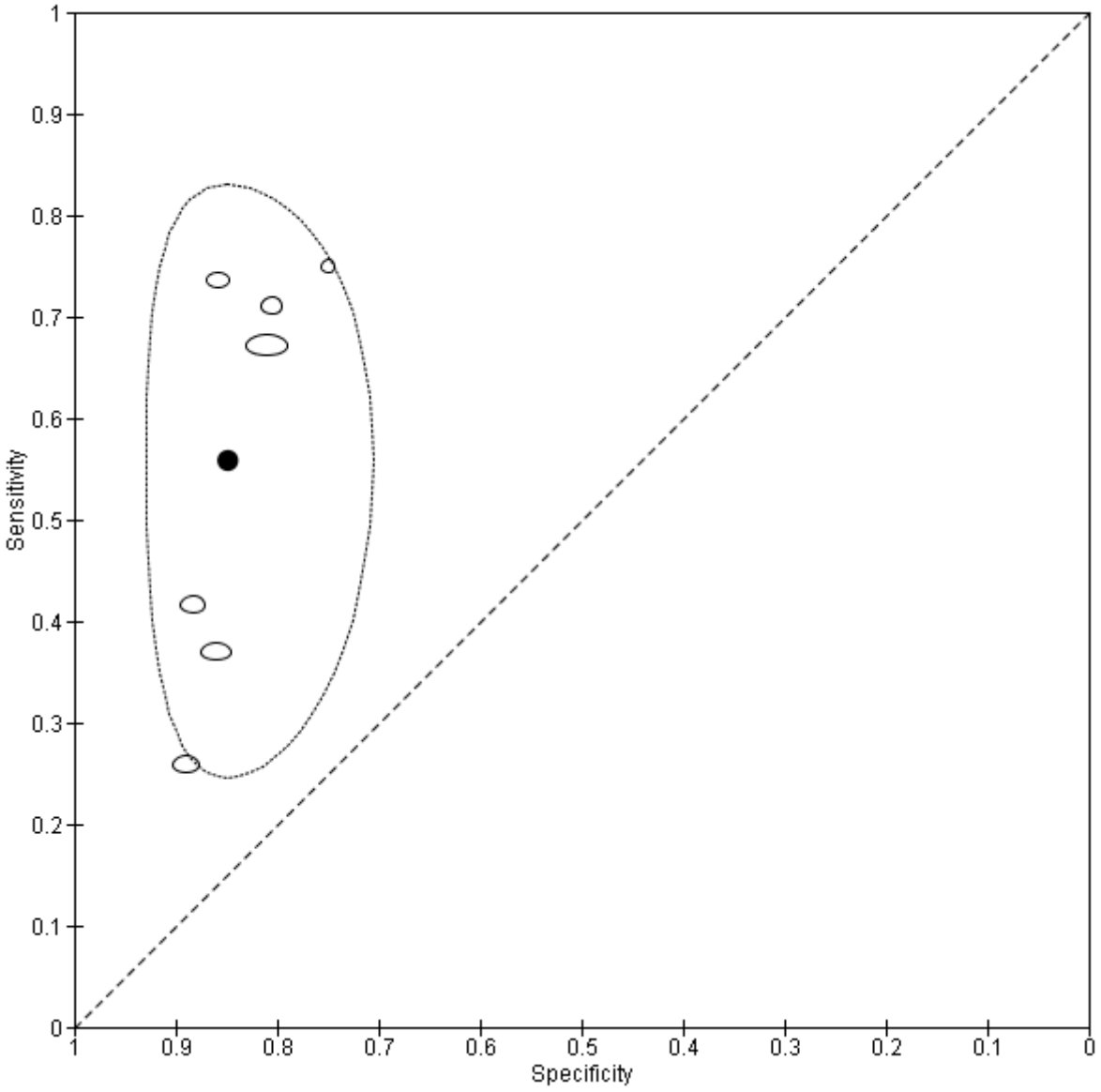


Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Kawamura 2013	6	3	2	9	0.98	0.75 [0.35, 0.97]	0.75 [0.43, 0.95]		
Kruger 2011	14	13	5	79	0.98	0.74 [0.49, 0.91]	0.86 [0.77, 0.92]		
McPherson 2010	7	13	20	105	1.0	0.26 [0.11, 0.46]	0.89 [0.82, 0.94]		
Pathik 2015	27	14	11	58	1.0	0.71 [0.54, 0.85]	0.81 [0.70, 0.89]		
Perez 2013	10	28	17	173	1.0	0.37 [0.19, 0.58]	0.86 [0.80, 0.91]		
Sumida 2012	43	97	21	415	1.0	0.67 [0.54, 0.78]	0.81 [0.77, 0.84]		
Xun 2012	10	15	14	113	1.0	0.42 [0.22, 0.63]	0.88 [0.81, 0.93]		



3

Figure 89: Diagnostic meta-analysis of APRI at a threshold of 0.98–1 for diagnosing advanced fibrosis

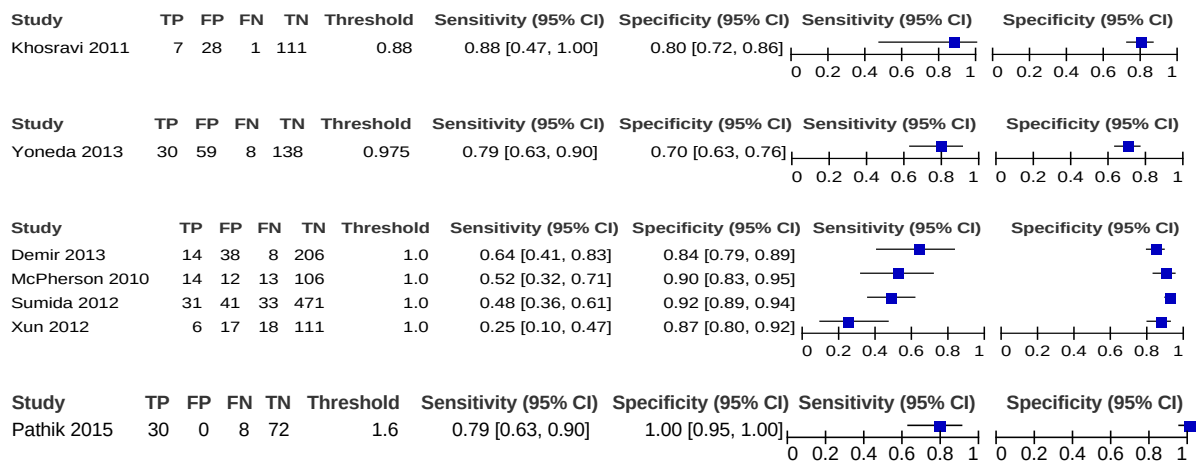


1

Figure 90: AST/ALT ratio for diagnosing advanced fibrosis at increasing thresholds from 0.67 to 1.6

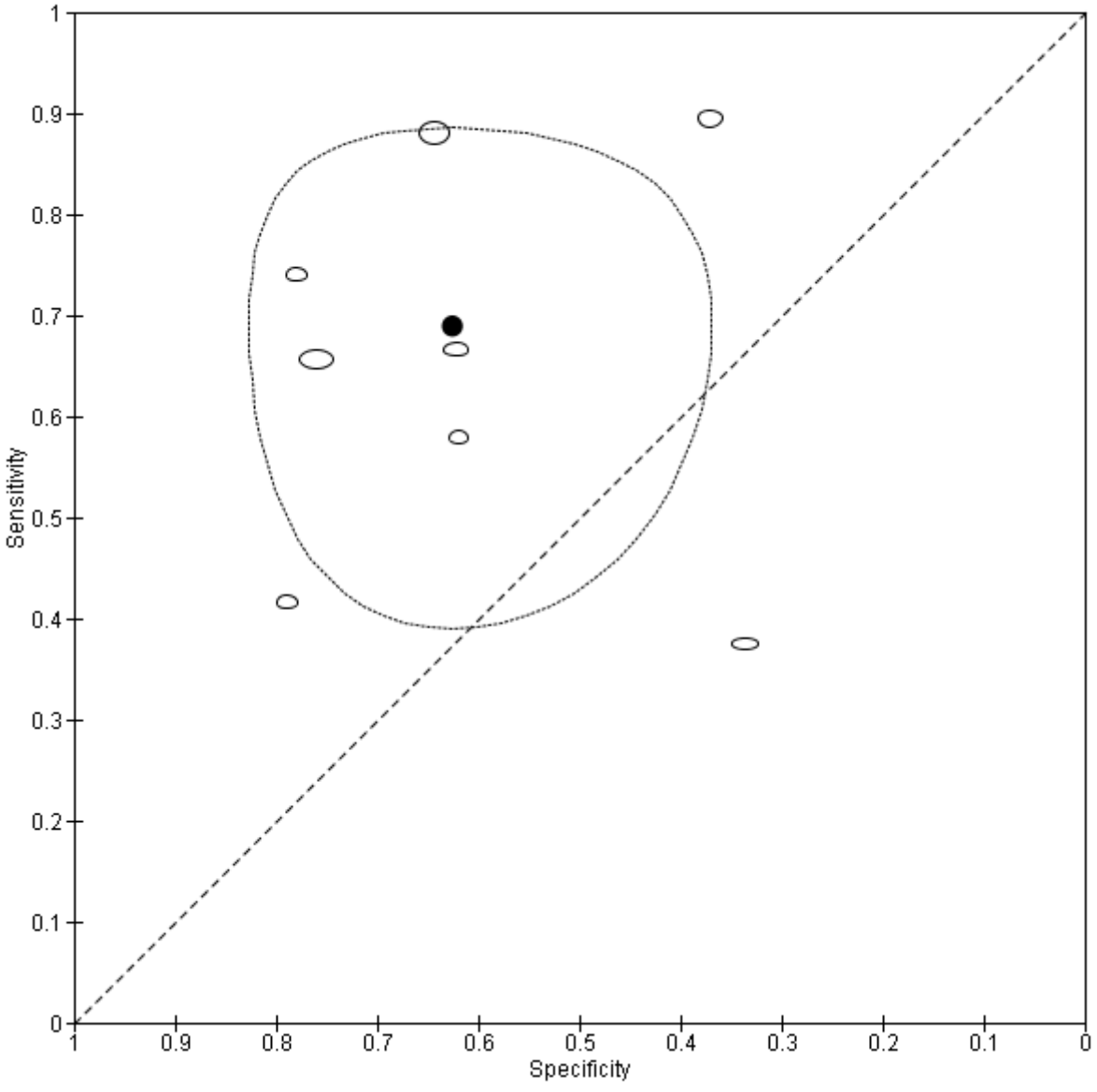
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dvorak 2014	11	13	6	26	0.67	0.65 [0.38, 0.86]	0.67 [0.50, 0.81]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Demir 2013	6	162	10	82	0.8	0.38 [0.15, 0.65]	0.34 [0.28, 0.40]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1
Goh 2015	118	124	16	224	0.8	0.88 [0.81, 0.93]	0.64 [0.59, 0.69]		
Kruger 2011	11	35	8	57	0.8	0.58 [0.33, 0.80]	0.62 [0.51, 0.72]		
McPherson 2010	20	26	7	92	0.8	0.74 [0.54, 0.89]	0.78 [0.69, 0.85]		
Perez 2013	18	76	9	125	0.8	0.67 [0.46, 0.83]	0.62 [0.55, 0.69]		
Sumida 2012	42	123	22	389	0.8	0.66 [0.53, 0.77]	0.76 [0.72, 0.80]		
Xun 2012	10	27	14	101	0.8	0.42 [0.22, 0.63]	0.79 [0.71, 0.86]		
Yoneda 2013	34	124	4	73	0.8	0.89 [0.75, 0.97]	0.37 [0.30, 0.44]		



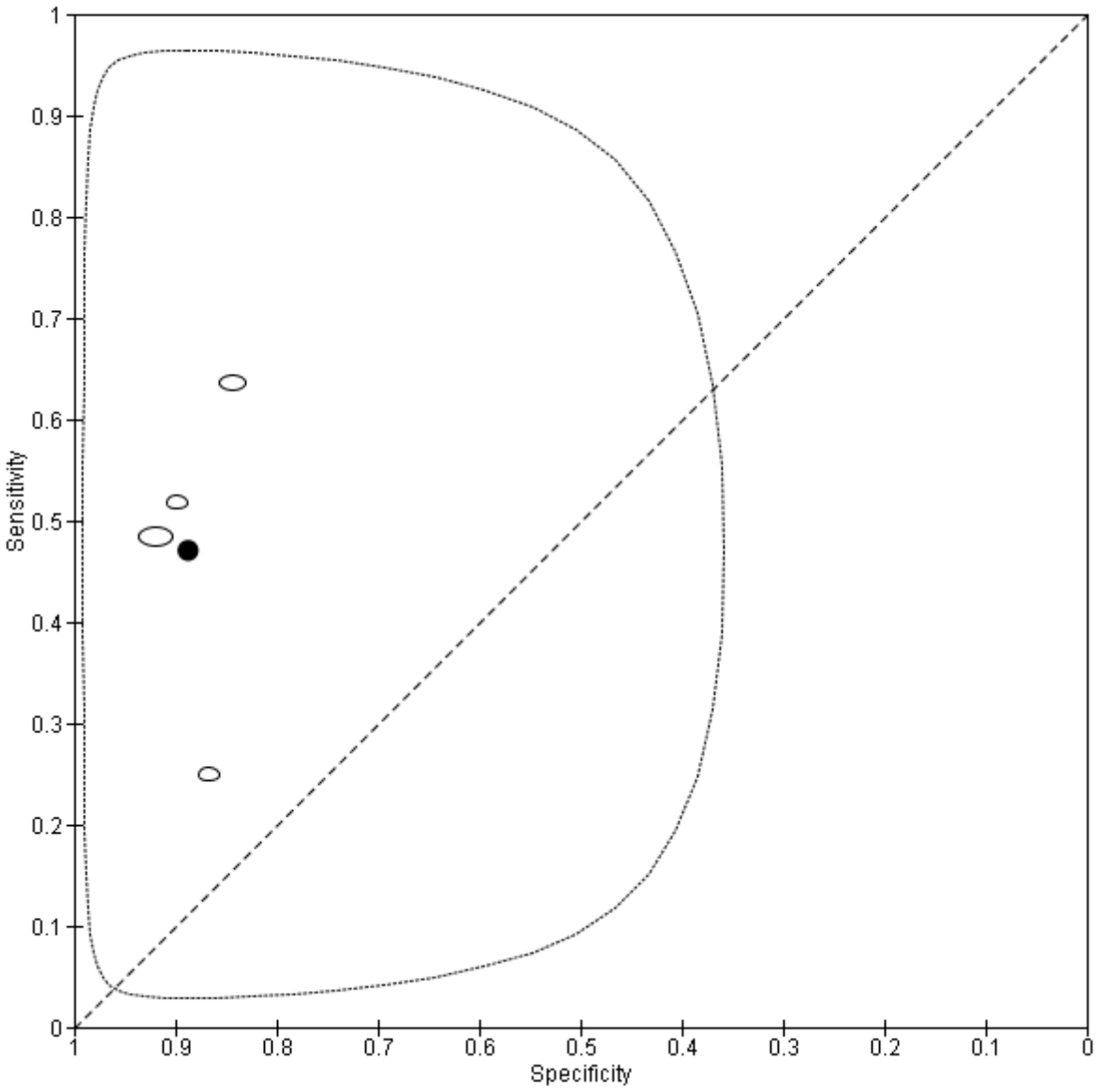
1

Figure 91: Diagnostic meta-analysis of AST/ALT ratio at a threshold of 0.8 for diagnosing advanced fibrosis



1

Figure 92: Diagnostic meta-analysis of AST/ALT ratio at a threshold of 1 for diagnosing advanced fibrosis



2

Figure 93: BARD for diagnosing advanced fibrosis

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Adams 2011	32	54	21	135	2.0	0.60 [0.46, 0.74]	0.71 [0.64, 0.78]
Cichoz-Lach 2012	24	11	3	88	2.0	0.89 [0.71, 0.98]	0.89 [0.81, 0.94]
Demir 2013	14	101	6	121	2.0	0.70 [0.46, 0.88]	0.55 [0.48, 0.61]
Goh 2015	118	197	16	150	2.0	0.88 [0.81, 0.93]	0.43 [0.38, 0.49]
Kawamura 2013	7	2	1	10	2.0	0.88 [0.47, 1.00]	0.83 [0.52, 0.98]
Lee 2013	34	48	0	25	2.0	1.00 [0.90, 1.00]	0.34 [0.24, 0.46]
McPherson 2010	24	65	3	53	2.0	0.89 [0.71, 0.98]	0.45 [0.36, 0.54]
Perez 2013	21	115	6	86	2.0	0.78 [0.58, 0.91]	0.43 [0.36, 0.50]
Raszeja 2010	13	24	2	64	2.0	0.87 [0.60, 0.98]	0.73 [0.62, 0.82]
Ruffillo 2011	19	23	18	78	2.0	0.51 [0.34, 0.68]	0.77 [0.68, 0.85]
Shah 2009	91	163	34	253	2.0	0.73 [0.64, 0.80]	0.61 [0.56, 0.66]
Sumida 2012	51	179	13	333	2.0	0.80 [0.68, 0.89]	0.65 [0.61, 0.69]
Xun 2012	10	27	14	101	2.0	0.42 [0.22, 0.63]	0.79 [0.71, 0.86]
Yoneda 2013	33	133	5	64	2.0	0.87 [0.72, 0.96]	0.32 [0.26, 0.40]

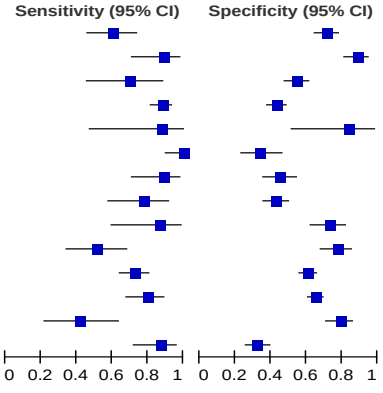


Figure 94: Diagnostic meta-analysis of BARD at a threshold of 2 for diagnosing advanced fibrosis

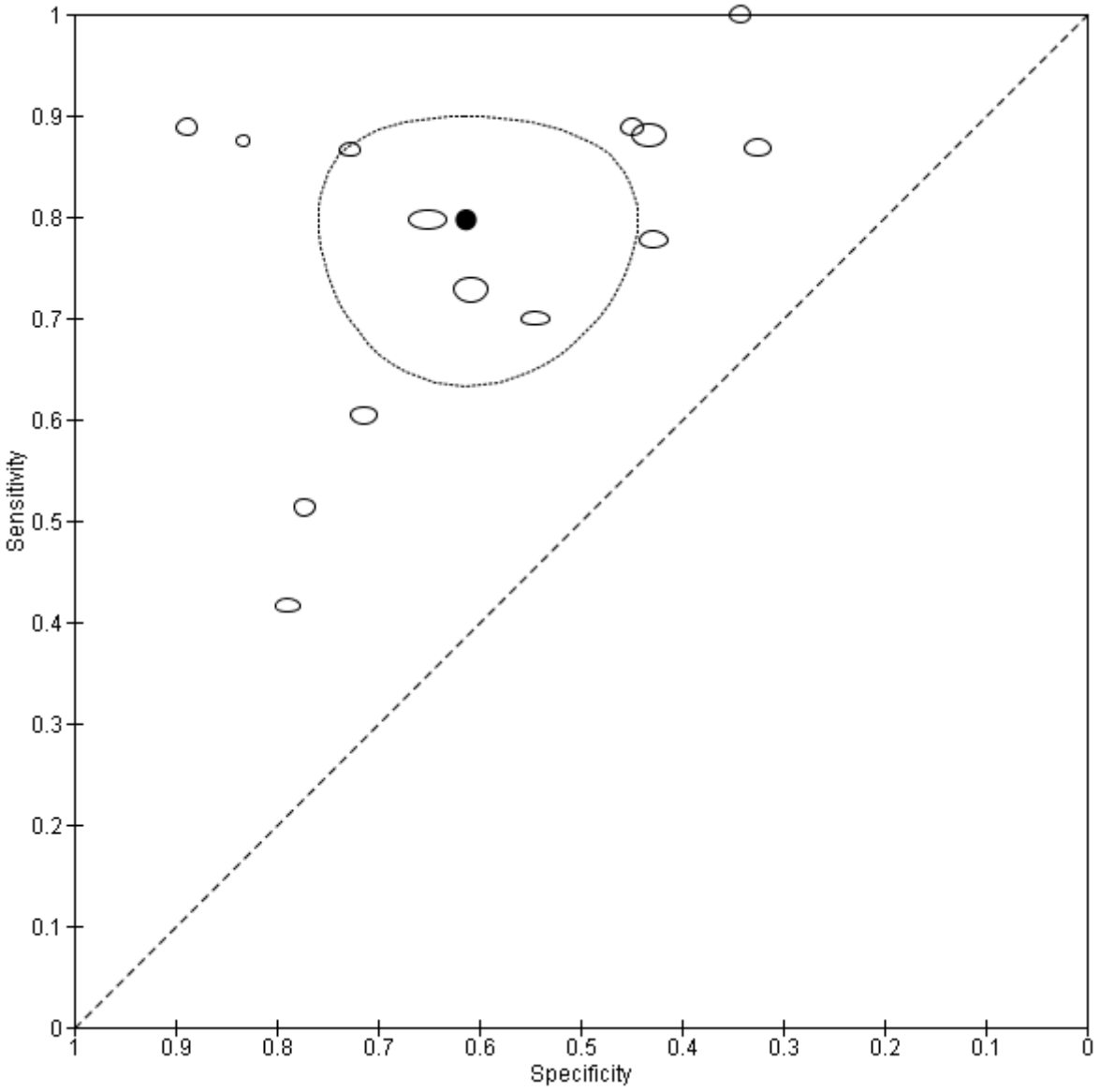
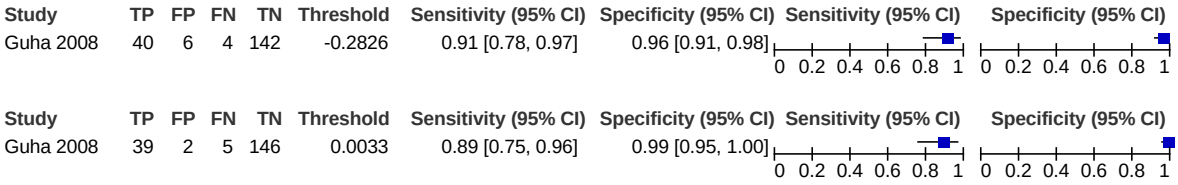


Figure 95: ELF for diagnosing advanced fibrosis at increasing thresholds from -3.37 to 10.51

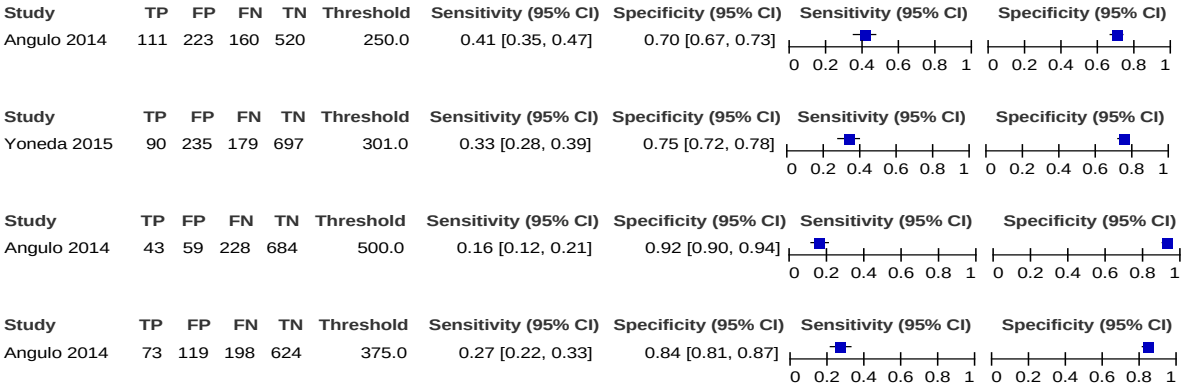
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dvorak 2014	15	1	2	38	-3.37	0.88 [0.64, 0.99]	0.97 [0.87, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1
Guha 2008	35	15	9	133	0.3576	0.80 [0.65, 0.90]	0.90 [0.84, 0.94]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1
Nobili 2008	8	2	0	102	10.51	1.00 [0.63, 1.00]	0.98 [0.93, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Figure 96: ELF + NAFLD fibrosis score for diagnosing advanced fibrosis at increasing thresholds from -0.2826 to 0.0033



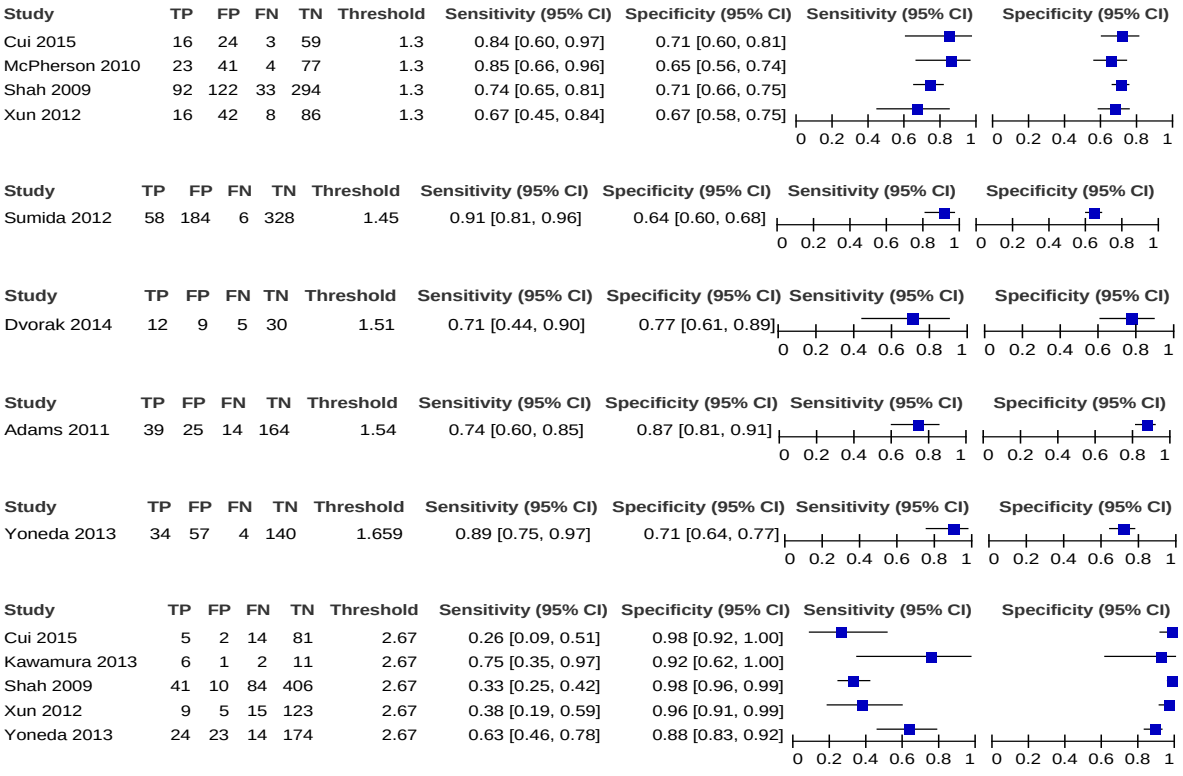
1

Figure 97: Ferritin for diagnosing advanced fibrosis at increasing thresholds from 250 to 500

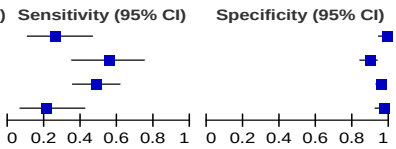


2

Figure 98: FIB4 for diagnosing advanced fibrosis at increasing thresholds from 1.3 to 3.25

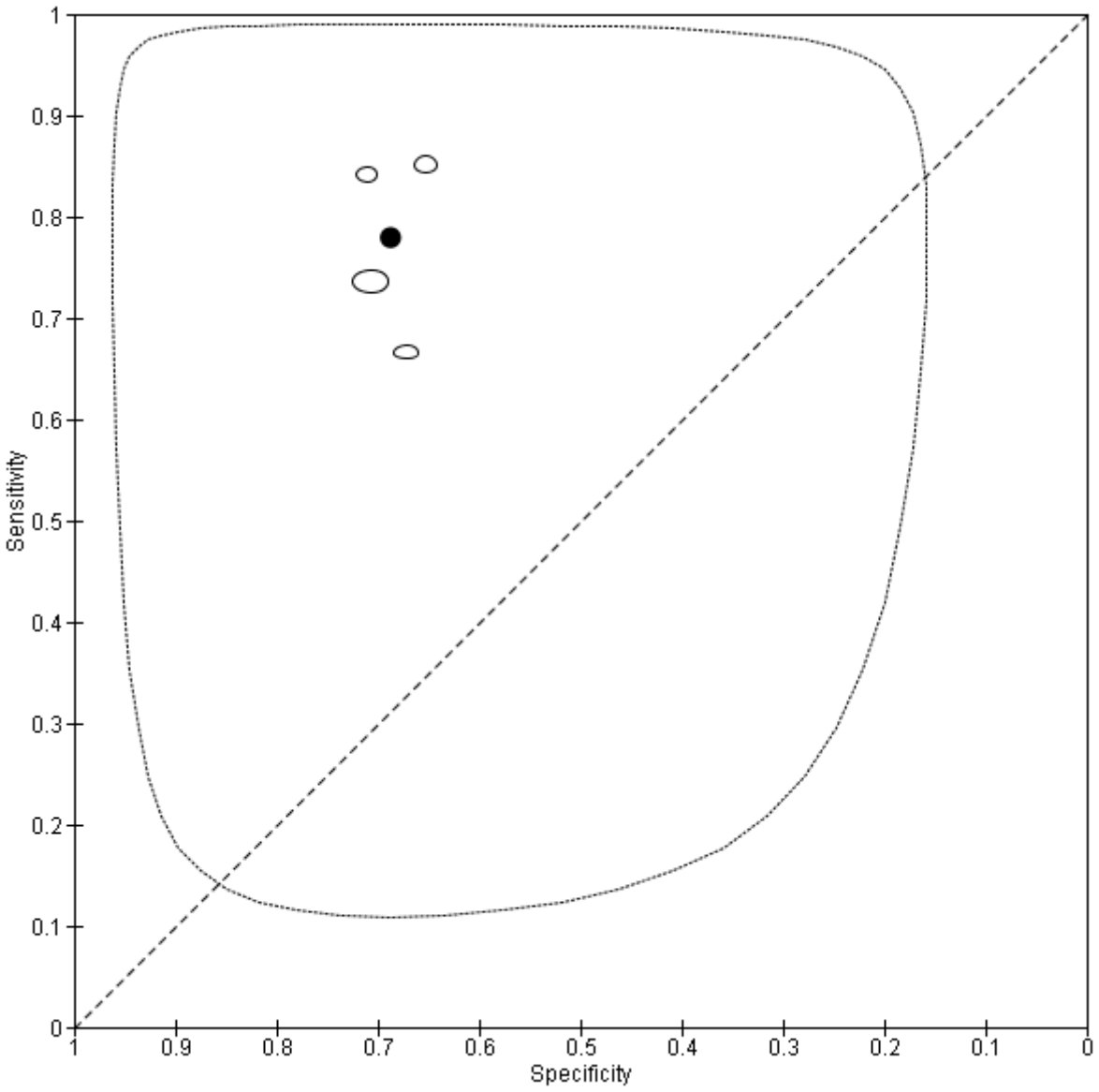


Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
McPherson 2010	7	2	20	116	3.25	0.26 [0.11, 0.46]	0.98 [0.94, 1.00]
Perez 2013	15	22	12	179	3.25	0.56 [0.35, 0.75]	0.89 [0.84, 0.93]
Sumida 2012	31	26	33	486	3.25	0.48 [0.36, 0.61]	0.95 [0.93, 0.97]
Xun 2012	5	4	19	124	3.25	0.21 [0.07, 0.42]	0.97 [0.92, 0.99]



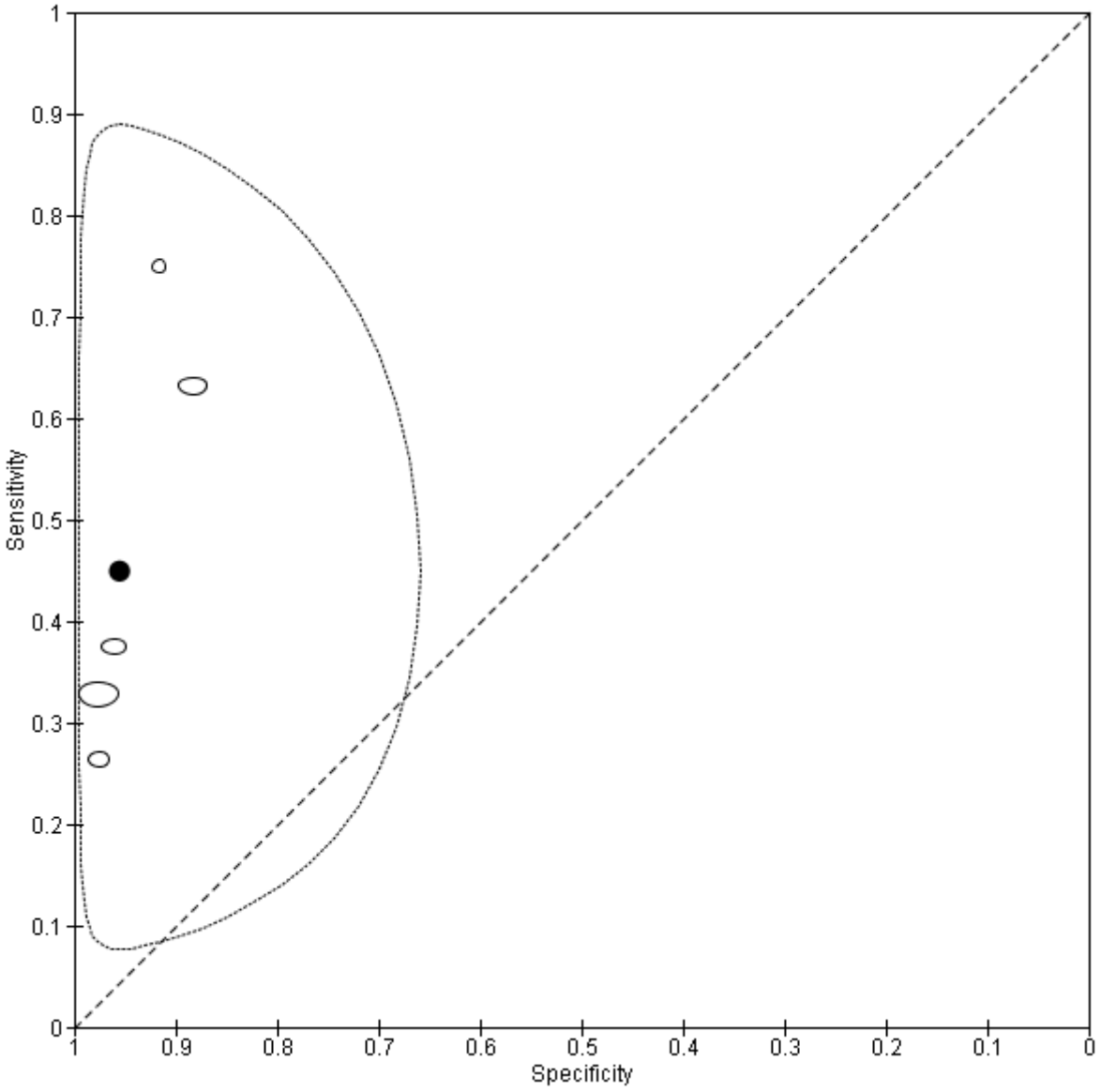
1

Figure 99: Diagnostic meta-analysis of FIB4 at a threshold of 1.3 for diagnosing advanced fibrosis



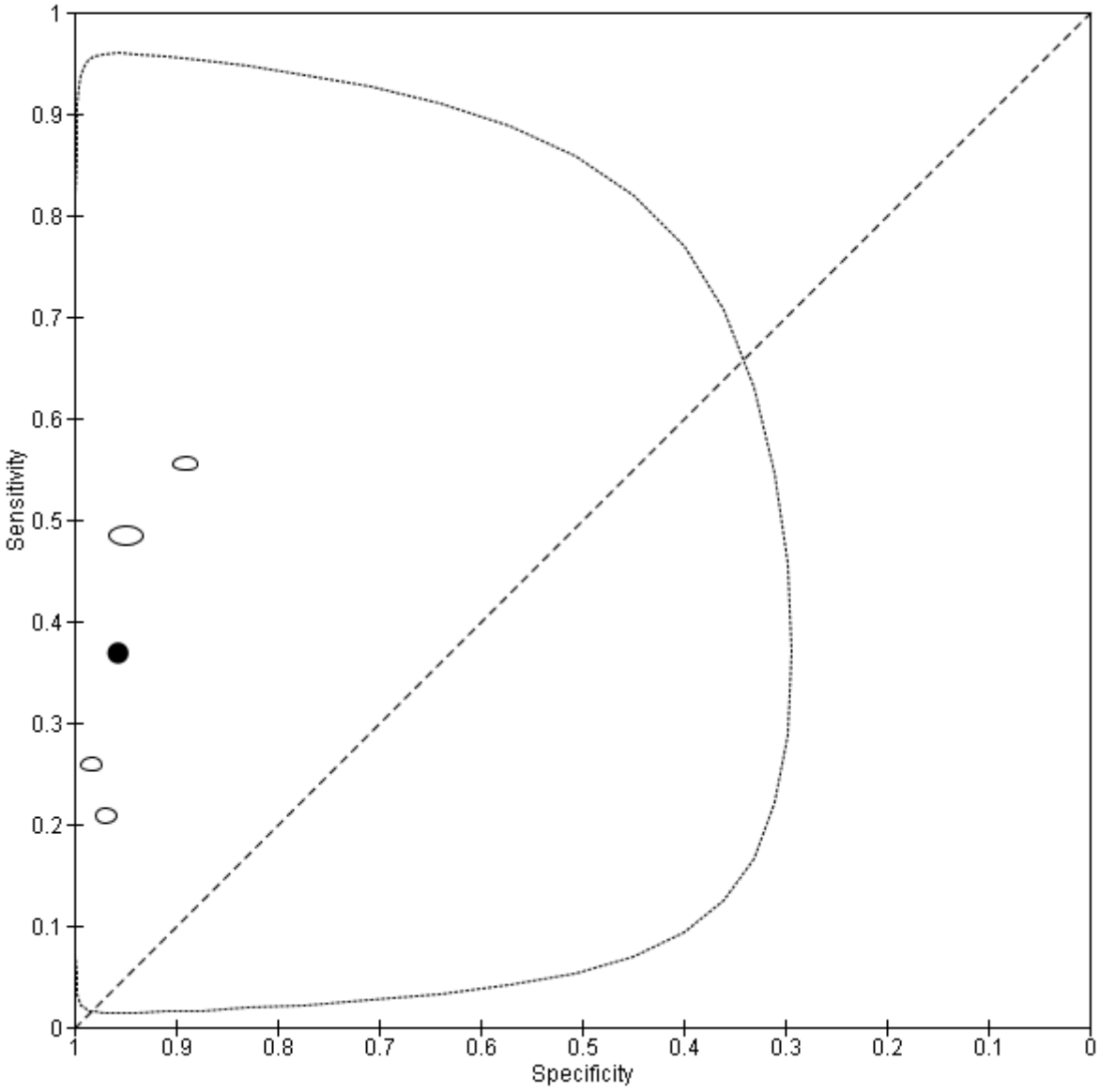
2

Figure 100: Diagnostic meta-analysis of FIB4 at a threshold of 2.67 for diagnosing advanced fibrosis



1

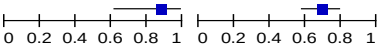
Figure 101: Diagnostic meta-analysis of FIB4 at a threshold of 3.25 for diagnosing advanced fibrosis



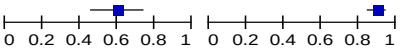
1

Figure 102: Fibrotest for diagnosing advanced fibrosis at increasing thresholds from 0.3 to 0.7

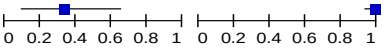
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ratziu 2006 (study 1)	19	43	1	107	0.3	0.95 [0.75, 1.00]	0.71 [0.63, 0.78]		
Ratziu 2009 (study 2)	14	25	2	56	0.3	0.88 [0.62, 0.98]	0.69 [0.58, 0.79]		



Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Adams 2011	32	19	21	170	0.47	0.60 [0.46, 0.74]	0.90 [0.85, 0.94]		



Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ratziu 2006 (study 1)	5	4	15	146	0.7	0.25 [0.09, 0.49]	0.97 [0.93, 0.99]		
Ratziu 2009 (study 2)	4	1	8	80	0.7	0.33 [0.10, 0.65]	0.99 [0.93, 1.00]		



2

Figure 103: NAFLD fibrosis score for diagnosing fibrosis at increasing thresholds from -2.16 to 0.735

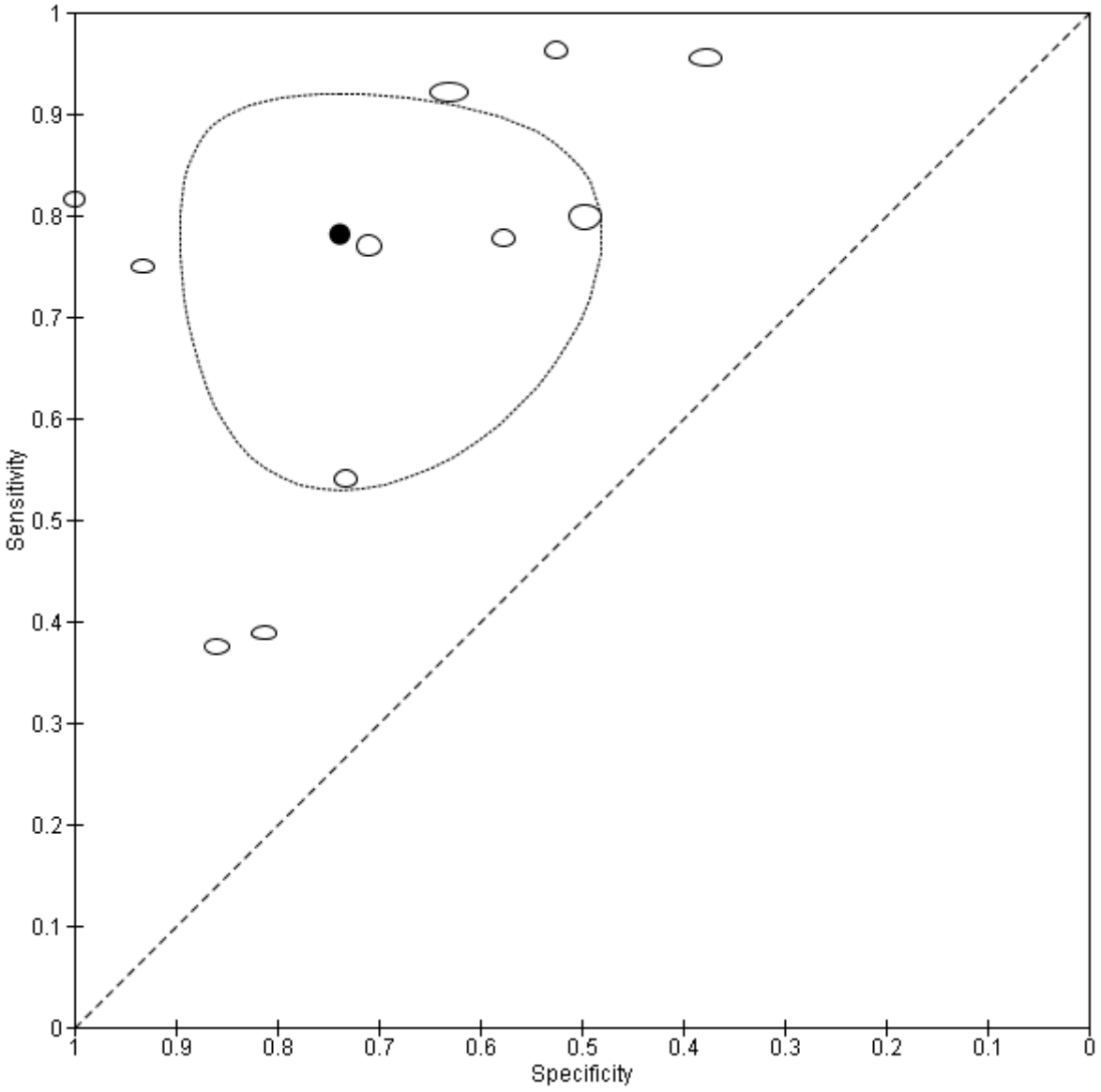
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Dvorak 2014	13	12	4	27	-2.16	0.76 [0.50, 0.93]	0.69 [0.52, 0.83]

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Angulo 2007	57	52	17	127	-1.455	0.77 [0.66, 0.86]	0.71 [0.64, 0.77]
Cichoz-Lach 2012	26	47	1	52	-1.455	0.96 [0.81, 1.00]	0.53 [0.42, 0.63]
Demir 2013	12	7	4	97	-1.455	0.75 [0.48, 0.93]	0.93 [0.87, 0.97]
Goh 2015	103	168	26	166	-1.455	0.80 [0.72, 0.86]	0.50 [0.44, 0.55]
McPherson 2010	21	50	6	68	-1.455	0.78 [0.58, 0.91]	0.58 [0.48, 0.67]
Pathik 2015	31	0	7	72	-1.455	0.82 [0.66, 0.92]	1.00 [0.95, 1.00]
Qureshi 2008	43	178	2	108	-1.455	0.96 [0.85, 0.99]	0.38 [0.32, 0.44]
Ruffillo 2011	20	27	17	74	-1.455	0.54 [0.37, 0.71]	0.73 [0.64, 0.82]
Sumida 2012	59	189	5	323	-1.455	0.92 [0.83, 0.97]	0.63 [0.59, 0.67]
Wong 2008	7	27	11	117	-1.455	0.39 [0.17, 0.64]	0.81 [0.74, 0.87]
Xun 2012	9	18	15	110	-1.455	0.38 [0.19, 0.59]	0.86 [0.79, 0.91]

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Angulo 2007	32	7	42	172	0.676	0.43 [0.32, 0.55]	0.96 [0.92, 0.98]
Cichoz-Lach 2012	24	10	3	89	0.676	0.89 [0.71, 0.98]	0.90 [0.82, 0.95]
Demir 2013	3	0	13	104	0.676	0.19 [0.04, 0.46]	1.00 [0.97, 1.00]
Goh 2015	50	26	79	308	0.676	0.39 [0.30, 0.48]	0.92 [0.89, 0.95]
McPherson 2010	9	2	18	116	0.676	0.33 [0.17, 0.54]	0.98 [0.94, 1.00]
Pathik 2015	38	22	0	50	0.676	1.00 [0.91, 1.00]	0.69 [0.57, 0.80]
Perez 2013	14	26	13	175	0.676	0.52 [0.32, 0.71]	0.87 [0.82, 0.91]
Qureshi 2008	22	45	23	241	0.676	0.49 [0.34, 0.64]	0.84 [0.80, 0.88]
Ruffillo 2011	5	0	32	101	0.676	0.14 [0.05, 0.29]	1.00 [0.96, 1.00]
Sumida 2012	21	20	43	492	0.676	0.33 [0.22, 0.46]	0.96 [0.94, 0.98]
Wong 2008	0	2	18	142	0.676	0.00 [0.00, 0.19]	0.99 [0.95, 1.00]
Xun 2012	2	0	22	128	0.676	0.08 [0.01, 0.27]	1.00 [0.97, 1.00]
Yoneda 2013	26	24	12	173	0.676	0.68 [0.51, 0.82]	0.88 [0.82, 0.92]

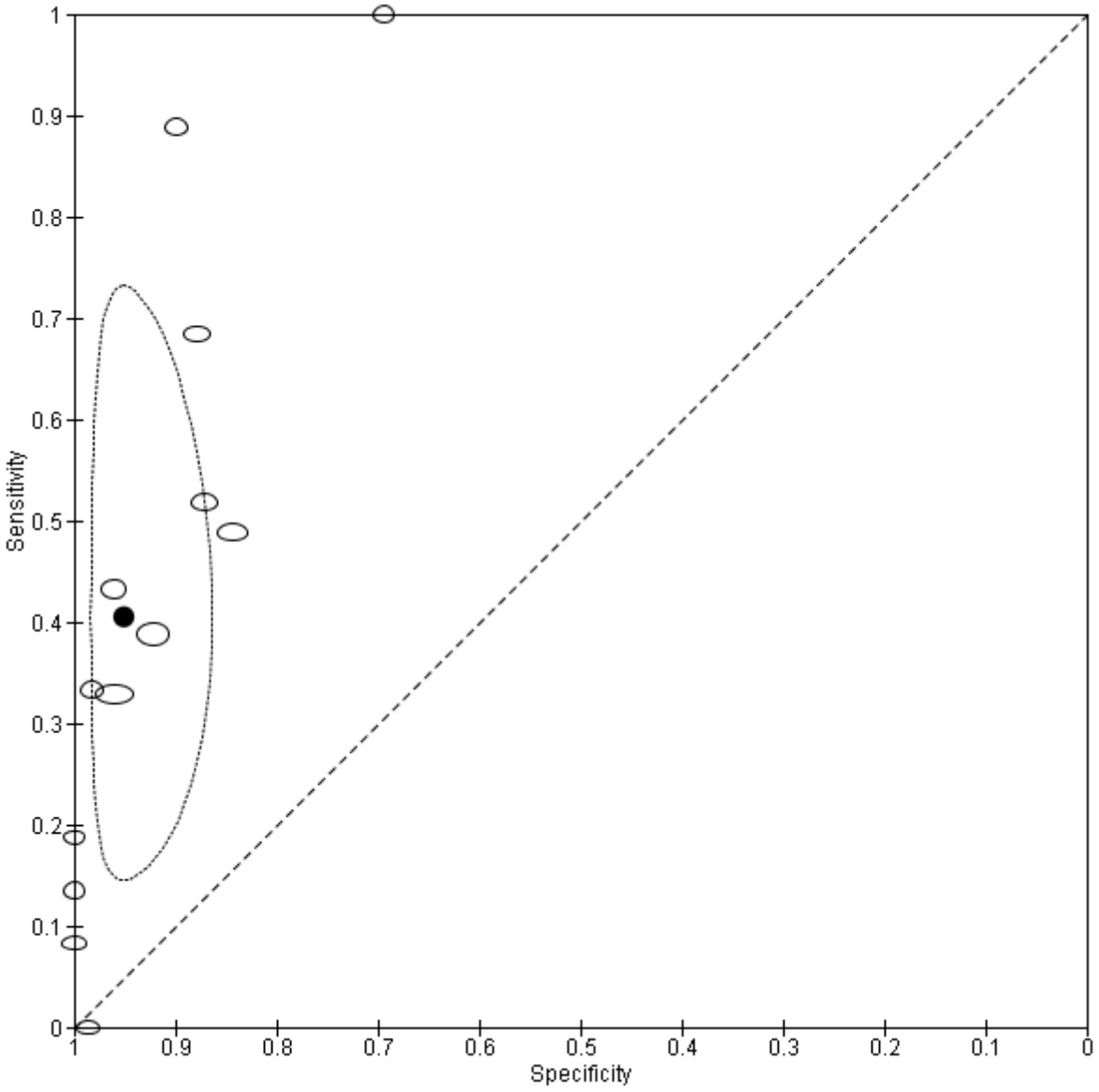
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Yoneda 2013	26	23	12	174	0.735	0.68 [0.51, 0.82]	0.88 [0.83, 0.92]

Figure 104: Diagnostic meta-analysis of NAFLD fibrosis score at a threshold of -1.455 for diagnosing advanced fibrosis



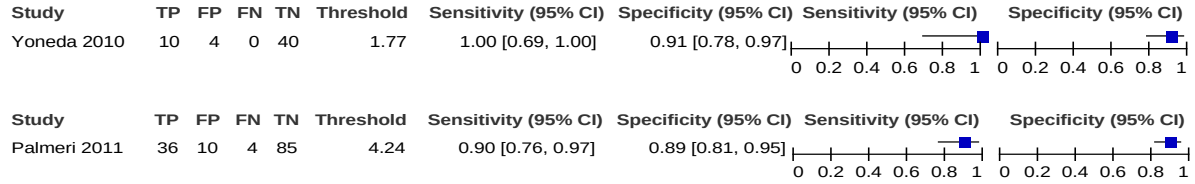
1

Figure 105: Diagnostic meta-analysis of NAFLD fibrosis score at a threshold of 0.676 for diagnosing advanced fibrosis



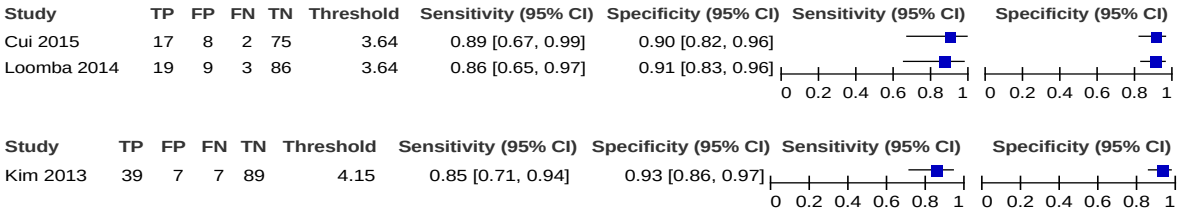
1

Figure 106: ARFI for diagnosing advanced fibrosis at increasing thresholds from 1.77 to 4.24



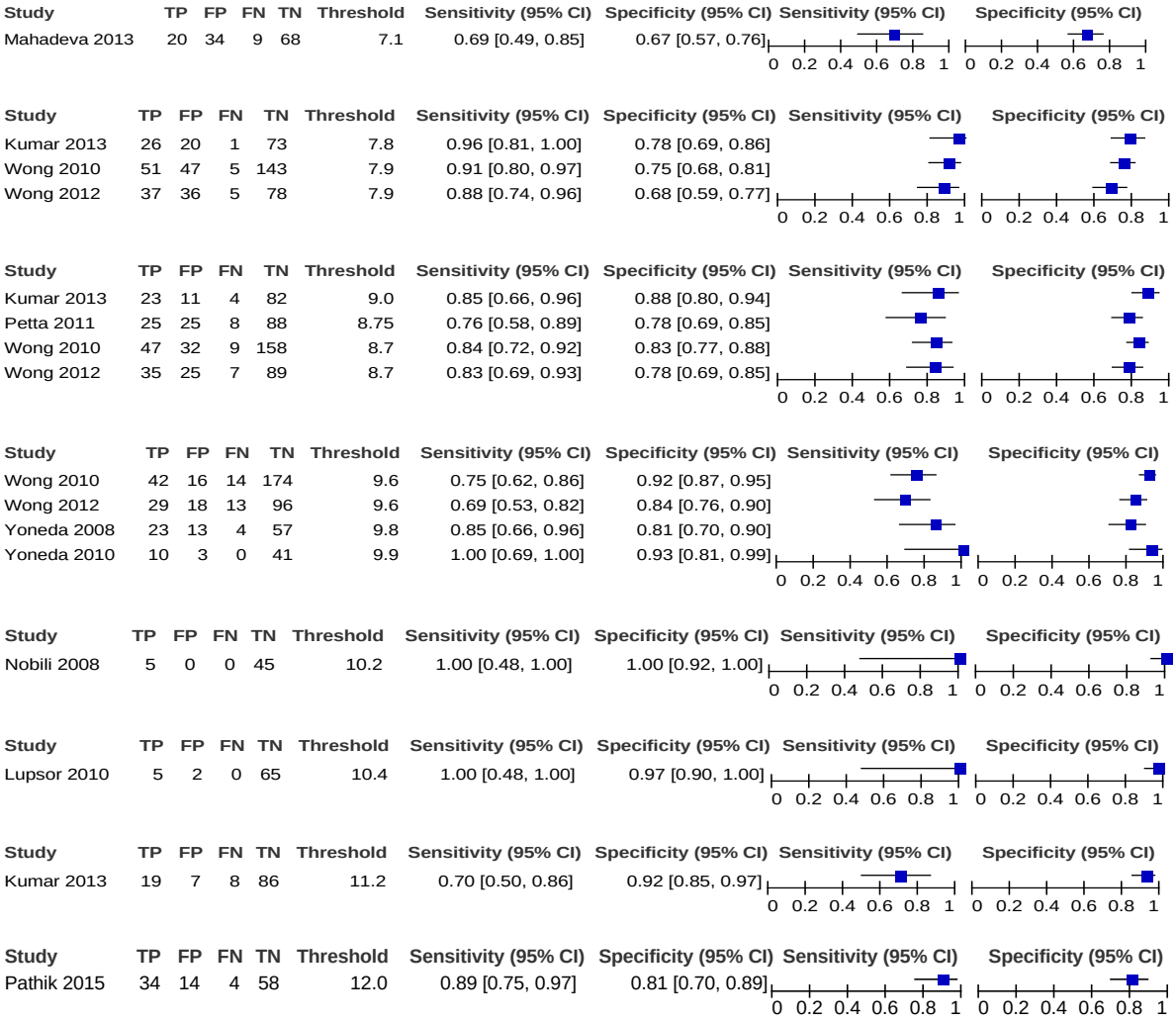
2

Figure 107: MR elastography for diagnosing advanced fibrosis at increasing thresholds from 3.64 to 4.15



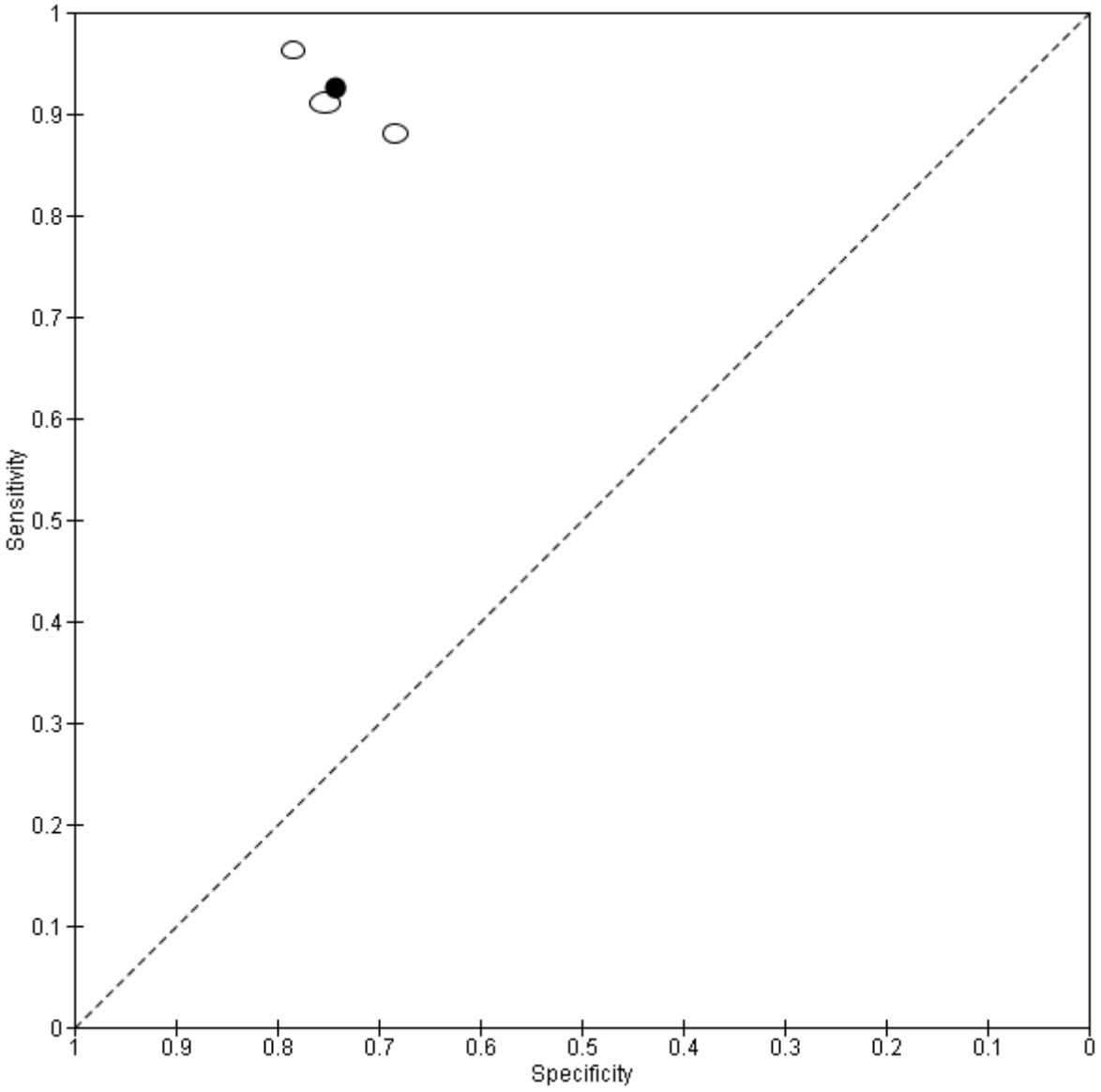
1

Figure 108: Transient elastography [M probe] for diagnosing advanced fibrosis at increasing thresholds from 7.8 to 12



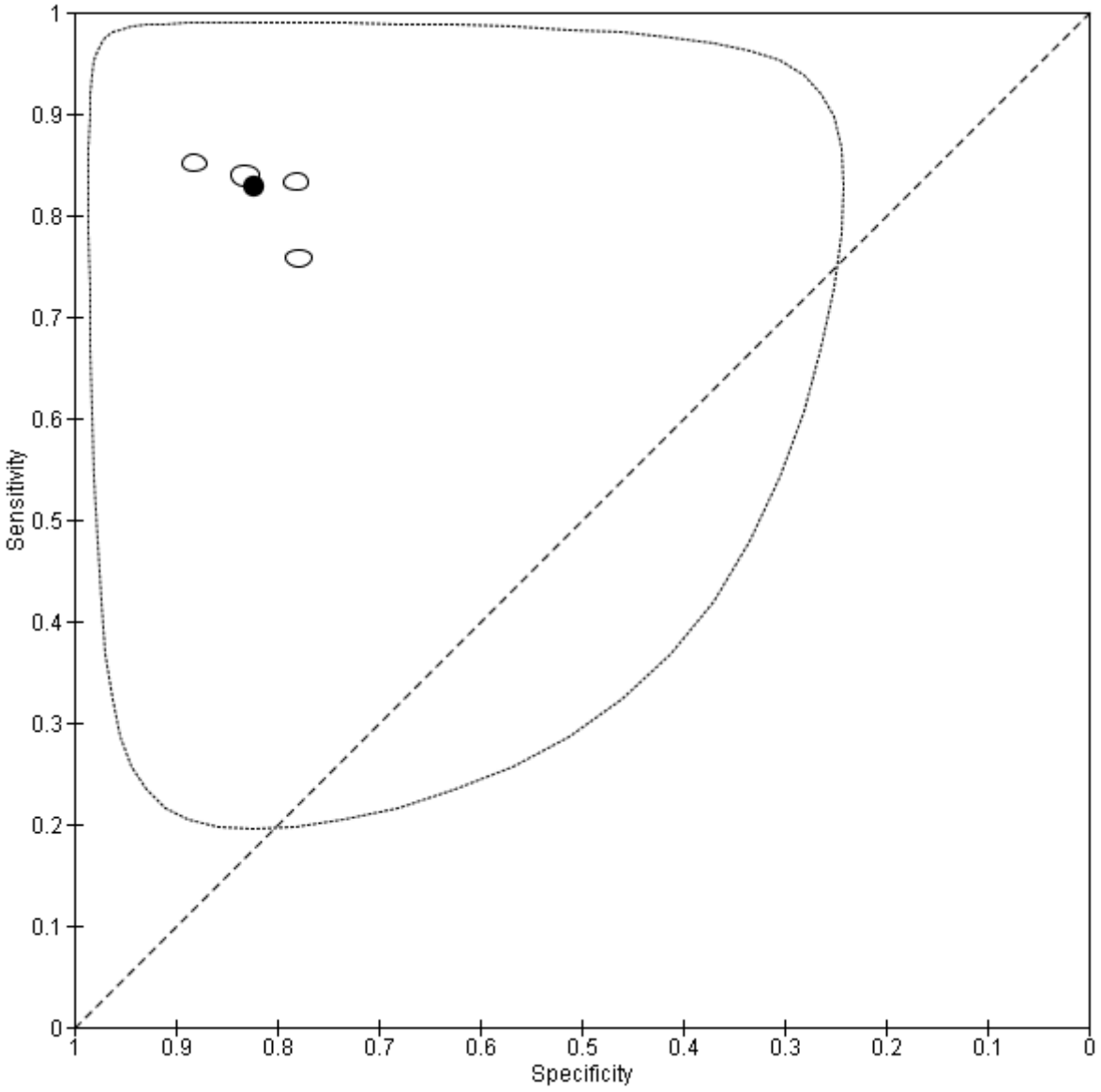
2

Figure 109: Diagnostic meta-analysis of transient elastography with the M probe at a threshold range of 7.8–7.9 kPa for diagnosing advanced fibrosis



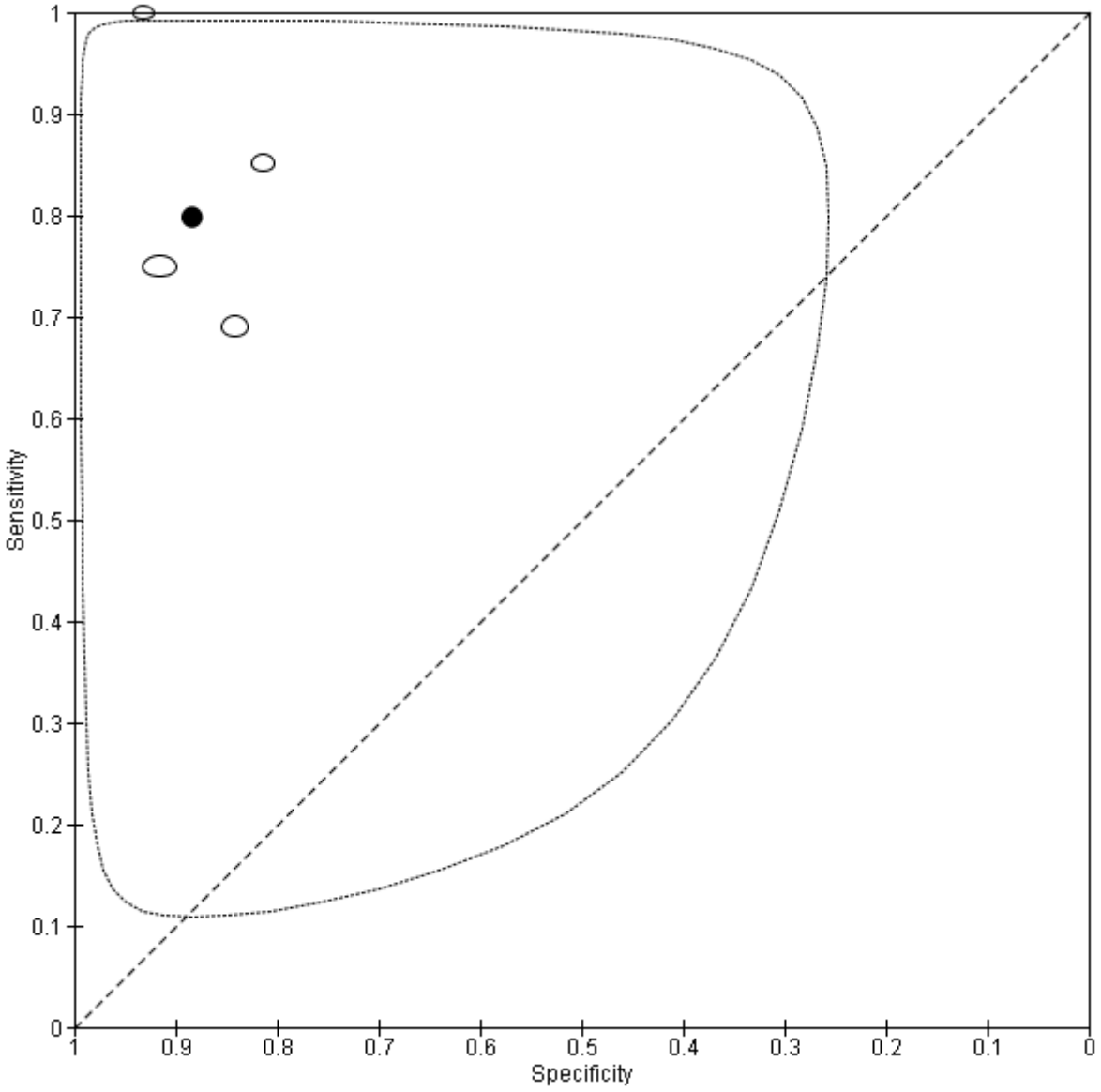
1

Figure 110: Diagnostic meta-analysis of transient elastography with the M probe at a threshold range of 8.7-9 kPa for diagnosing advanced fibrosis



1

Figure 111: Diagnostic meta-analysis of transient elastography with the M probe at a threshold range of 9.6-9.9 kPa for diagnosing advanced fibrosis



1

Figure 112: Transient elastography [XL probe] for diagnosing advanced fibrosis at increasing thresholds from 5.7 to 9.3

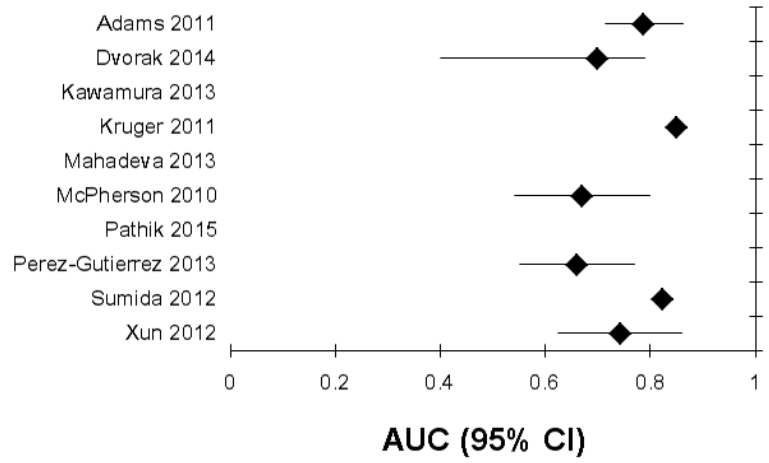
Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wong 2012	49	60	5	70	5.7	0.91 [0.80, 0.97]	0.54 [0.45, 0.63]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wong 2012	42	29	12	101	7.2	0.78 [0.64, 0.88]	0.78 [0.70, 0.85]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wong 2012	31	13	23	117	9.3	0.57 [0.43, 0.71]	0.90 [0.84, 0.95]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

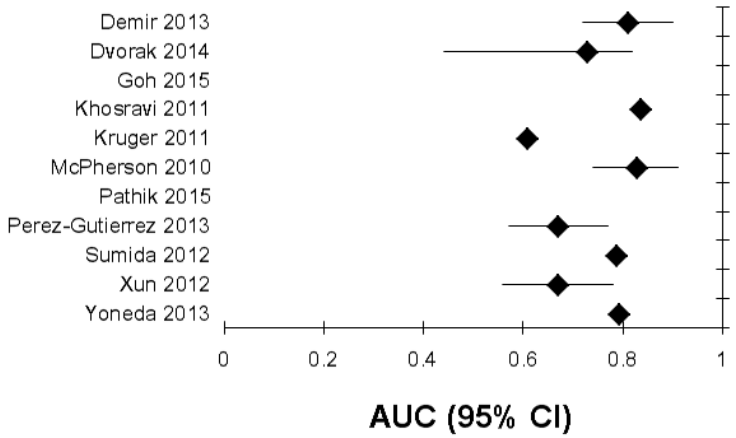
1K.3.3.2 Area under the curve plots

Figure 113: APRI advanced fibrosis



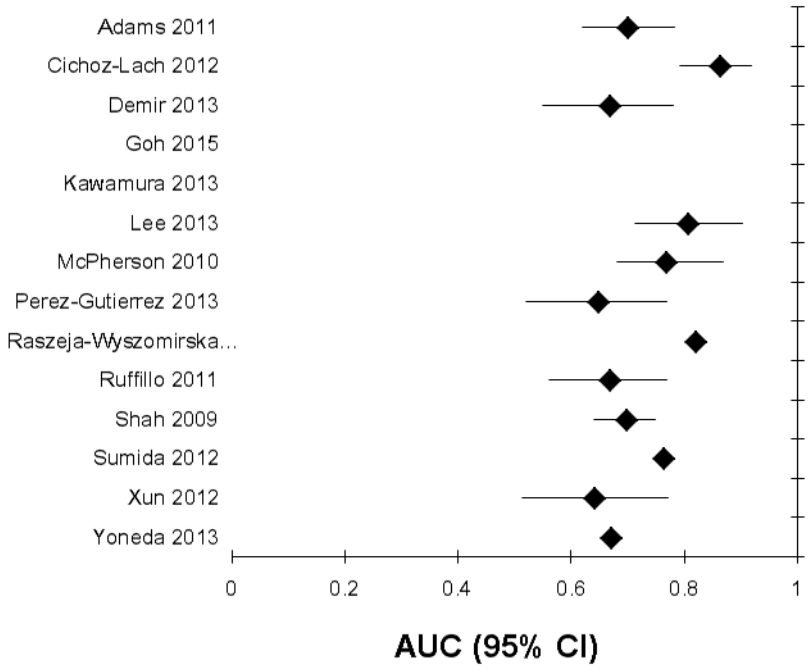
2

Figure 114: AST/ALT ratio advanced fibrosis



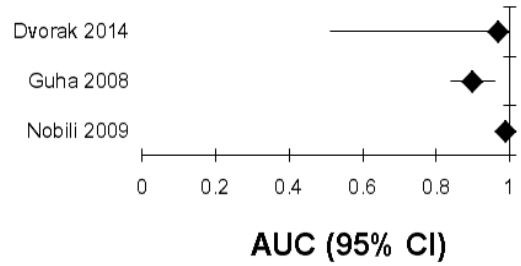
3

Figure 115: BARD advanced fibrosis



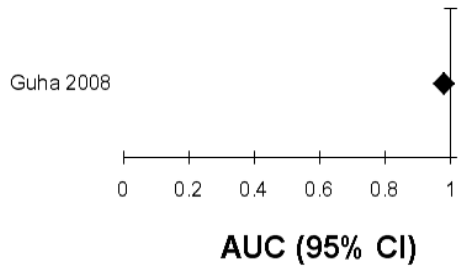
1

Figure 116: ELF advanced fibrosis



2

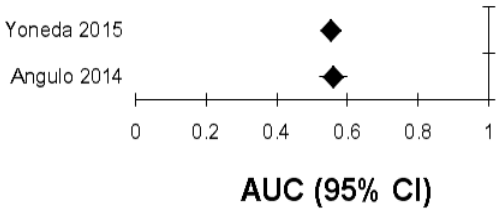
Figure 117: ELF + NAFLD fibrosis score advanced fibrosis



3

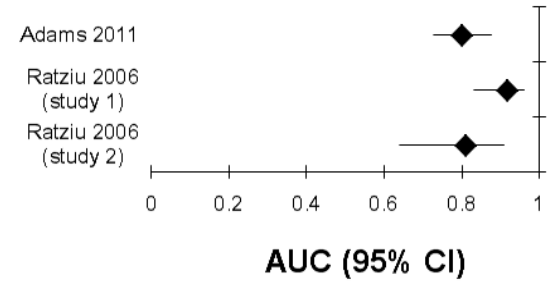
4

Figure 118: Ferritin advanced fibrosis



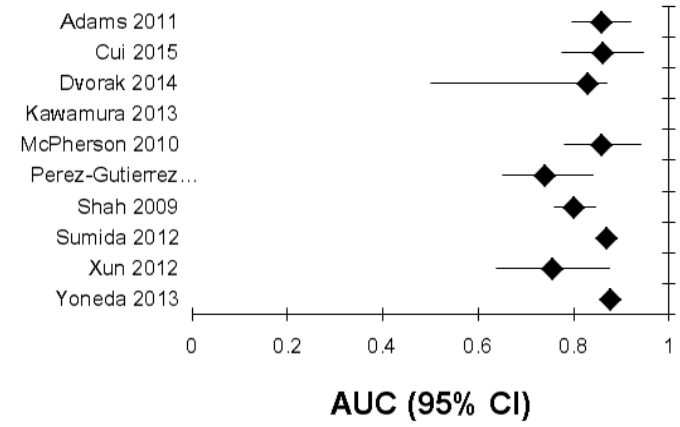
1

Figure 119: Fibrotest advanced fibrosis



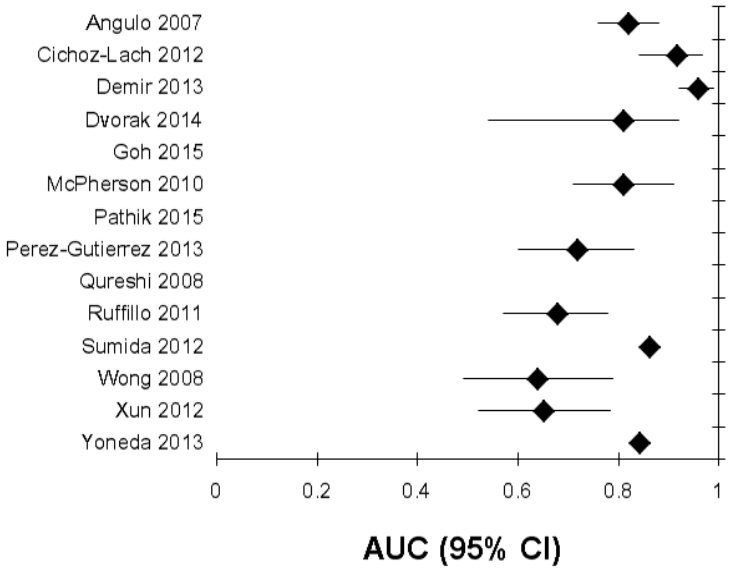
2

Figure 120: FIB4 advanced fibrosis



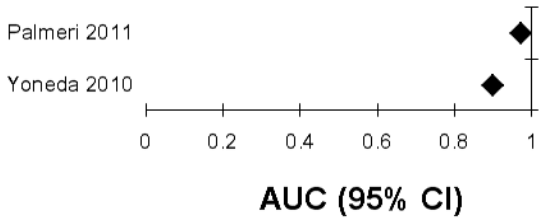
3

Figure 121: NAFLD fibrosis score advanced fibrosis



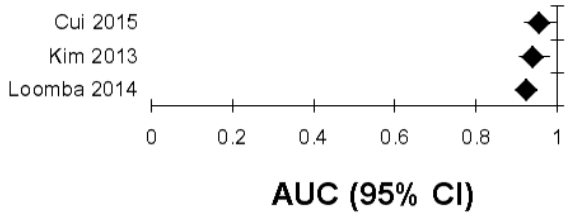
1

Figure 122: ARFI advanced fibrosis



2

Figure 123: MRE advanced fibrosis



3

Figure 124: TE advanced fibrosis

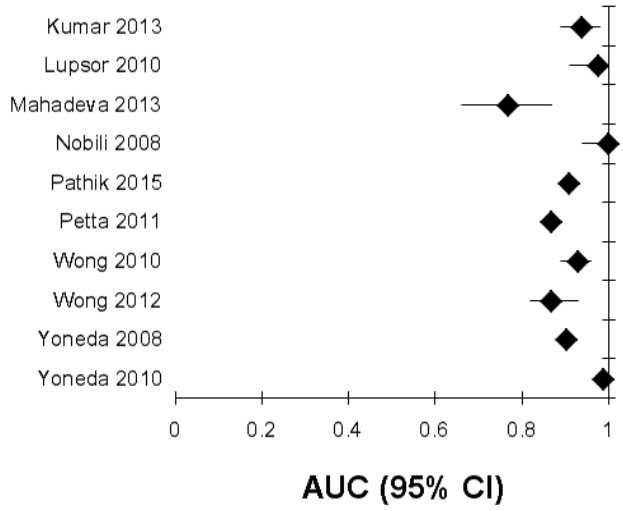
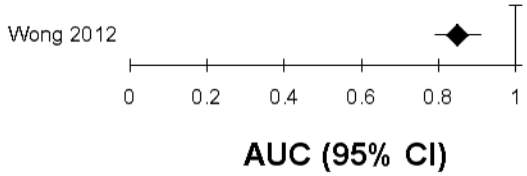


Figure 125: TE [XL probe] advanced fibrosis



K.4 Monitoring NAFLD progression

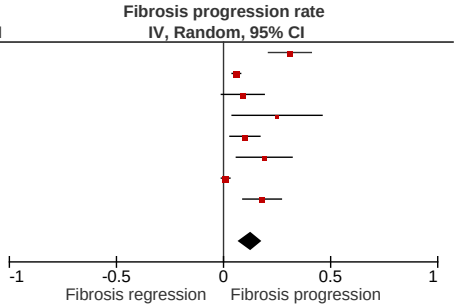
NB. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC practice.

K.4.1 Fibrosis progression rate: NAFLD patients (no fibrosis at baseline)

Figure 126: Fibrosis progression rate for NAFLD patients (no fibrosis at baseline)

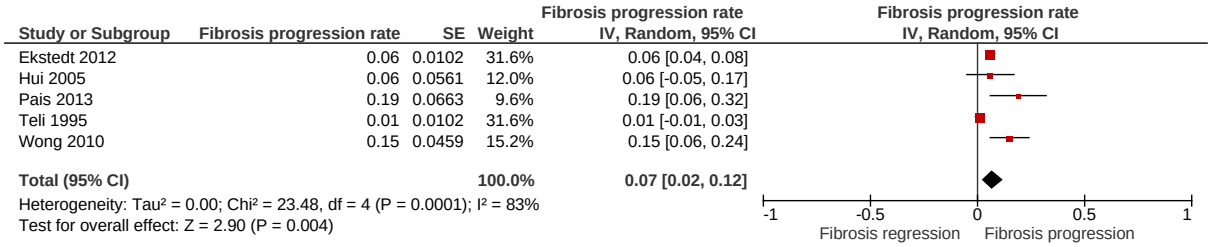
Study or Subgroup	Fibrosis progression rate	SE	Weight	Fibrosis progression rate IV, Random, 95% CI
Adams 2005	0.31	0.051	11.5%	0.31 [0.21, 0.41]
Ekstedt 2012	0.06	0.0102	18.2%	0.06 [0.04, 0.08]
Evans 2002	0.09	0.051	11.5%	0.09 [-0.01, 0.19]
Fassio 2004	0.25	0.1071	5.0%	0.25 [0.04, 0.46]
Hui 2005	0.1	0.0357	14.3%	0.10 [0.03, 0.17]
Pais 2013	0.19	0.0663	9.1%	0.19 [0.06, 0.32]
Teli 1995	0.01	0.0102	18.2%	0.01 [-0.01, 0.03]
Wong 2010	0.18	0.0459	12.4%	0.18 [0.09, 0.27]
Total (95% CI)			**100.0%**	**0.12 [0.07, 0.18]**

Heterogeneity: Tau² = 0.00; Chi² = 60.85, df = 7 (P < 0.00001); I² = 88%
Test for overall effect: Z = 4.48 (P < 0.00001)



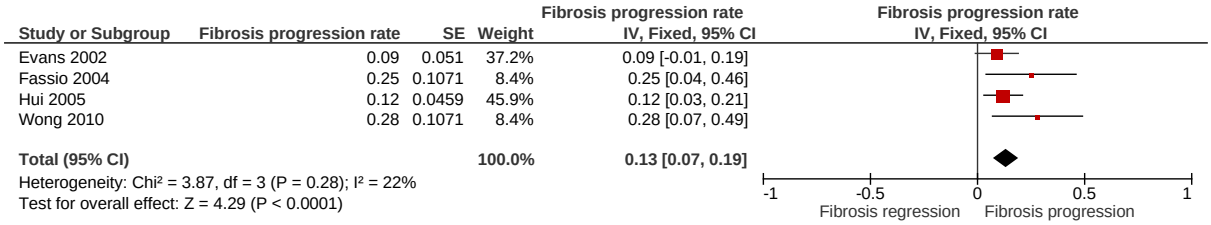
K.4.2 Fibrosis progression rate: NAFL patients (no fibrosis at baseline)

Figure 127: Fibrosis progression rate for NAFL patients (no fibrosis at baseline)



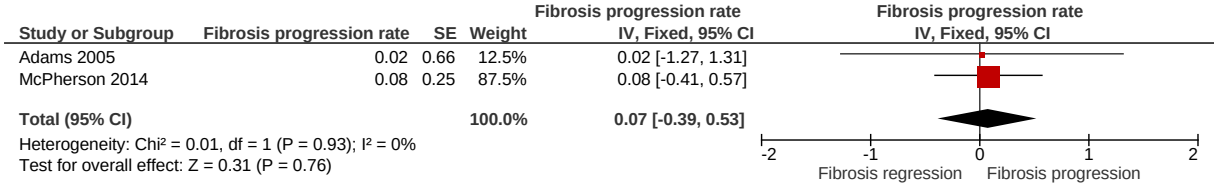
K.4.3 Fibrosis progression rate: NASH (no fibrosis at baseline)

Figure 128: Fibrosis progression rate for NASH patients (no fibrosis at baseline)



K.4.4 Fibrosis progression rate: NAFLD (any fibrosis baseline status)

Figure 129: Fibrosis progression rate for NAFLD patients (any fibrosis at baseline)



4

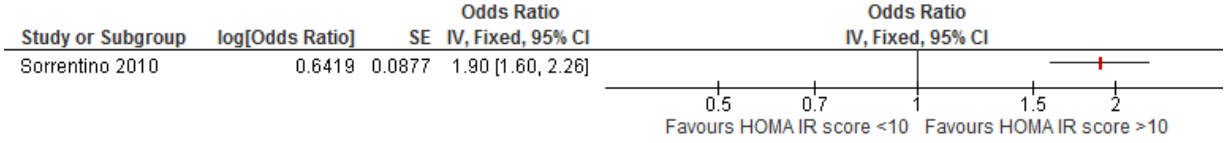
5 **Figure 130:**

6

7

K.4.5 Factors measured at baseline associated with change in biopsy fibrosis

Figure 131: HOMA-IR score>10 as a risk factor for fibrosis progression

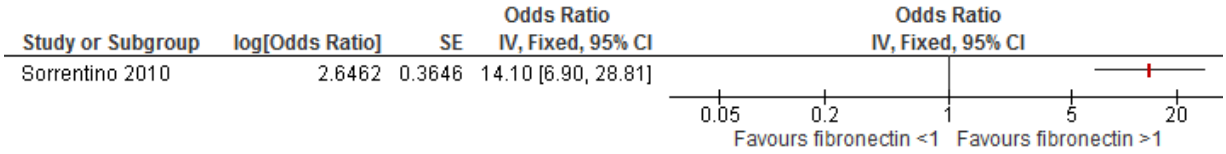


HOMA-IR=(fasting serum insulin level mU/l x plasma glucose level mmol/l)/22.5) (f) sex, age, BMI at baseline, presence of Mallory hyaline, hepatocyte ballooning, the grade of portal and lobular inflammation (grades 2 and 3 were combined), amount of fibronectin, the grade of Steatosis, diagnosis of NASH at baseline

Nb. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC centre practice.

1

Figure 132: Lobular deposition of fibronectin >1 at baseline as a risk factor for fibrosis progression

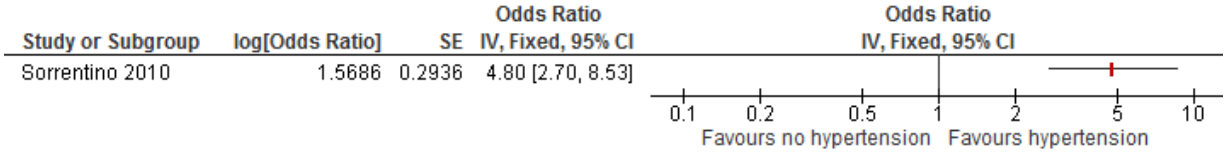


Adjusted in multivariate analysis for sex, age, BMI at baseline, presence of Mallory hyaline, hepatocyte ballooning, the grade of portal and lobular inflammation (grades 2 and 3 were combined), baseline HOMA IR score, the grade of Steatosis, diagnosis of NASH at baseline

Nb. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC centre practice.

2

Figure 133: Hypertension as a risk factor for fibrosis progression

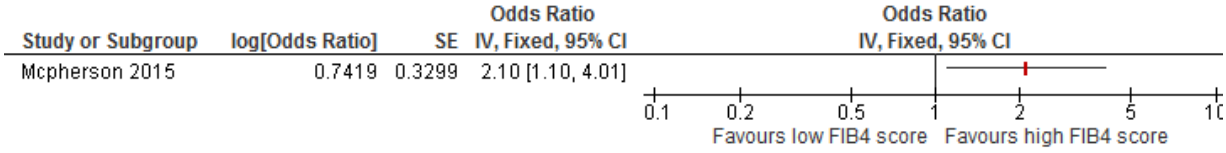


Adjusted in multivariate analysis for sex, age, BMI at baseline, presence of Mallory hyaline, hepatocyte ballooning, the grade of portal and lobular inflammation (grades 2 and 3 were combined), baseline HOMA IR, the grade of Steatosis, diagnosis of NASH at baseline

Nb. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC centre practice.

3

Figure 134: FIB-4 score at baseline as a risk factor for fibrosis progression

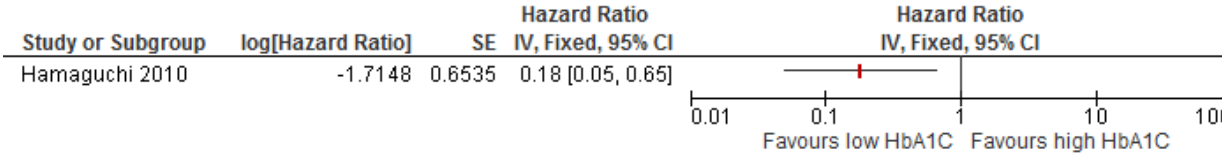


FIB-4 score = age = [years] × AST [IU/L]/platelet count [expressed as platelets × 10^9/L] × ($ALT^{1/2}$[IU/L]) [(b)] adjusted in multivariate analysis for baseline platelet count, AST/ALT ratio(alanine aminotransferase ratio/ Aspartate transaminase)

Nb. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC centre practice.

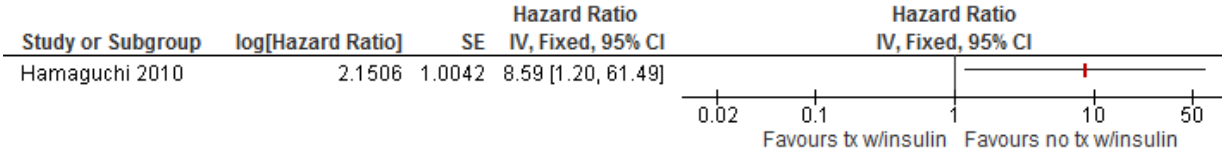
K.4.6 Factors measured at follow up associated with change in biopsy fibrosis

Figure 135: Change in HbA1C as a risk factor for fibrosis regression



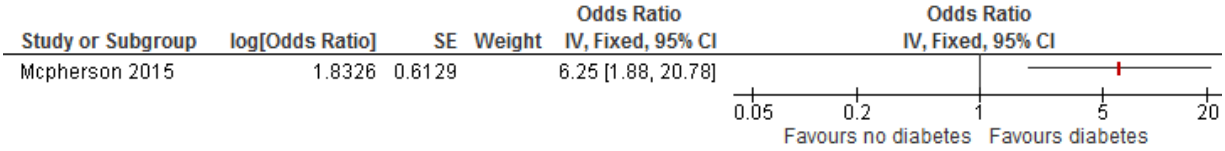
Adjusted in multivariate analysis for age, gender, BMI, treatment with insulin, baseline HbA1C levels

Figure 136: Treatment with insulin as a risk factor for fibrosis regression



Adjusted in multivariate analysis for age, gender, BMI, baseline HbA1C level, change in HbA1C level from baseline

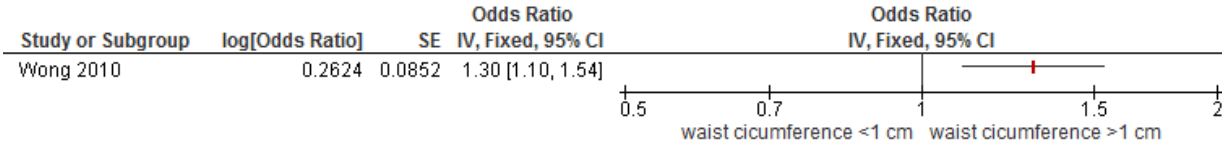
Figure 137: Diabetes type 2 as a risk factor for fibrosis progression



Adjusted in multivariate analysis for platelet count, GGT (Gamma-glutamyl transpeptidase), AST/ALT ratio (alanine aminotransferase ratio/ Aspartate transaminase), FIB4 score (FIB4 age = [years] × AST [IU/L]/platelet count [expressed as platelets × 10^9/L] × ($ALT^{1/2}$[IU/L]) , NAFLD progression score (NAFLD score-=-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl)

Nb. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC centre practice.

Figure 138: Change in waist circumference from baseline for predicting NAFLD progression (OR for each 1 cm increment)

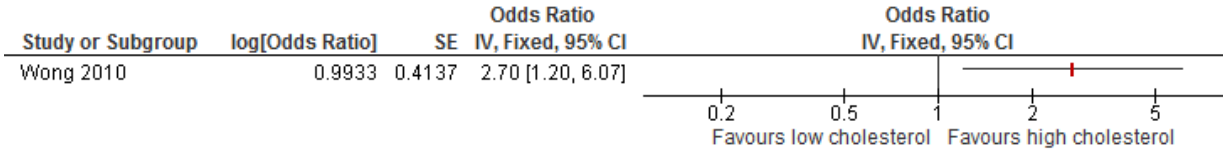


Adjusted in multivariate analysis using changes in BMI, ALT and low density lipoprotein-cholesterol level

Nb. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC centre practice.

1

Figure 139: High baseline low density lipoprotein-cholesterol as a risk factor for fibrosis progression

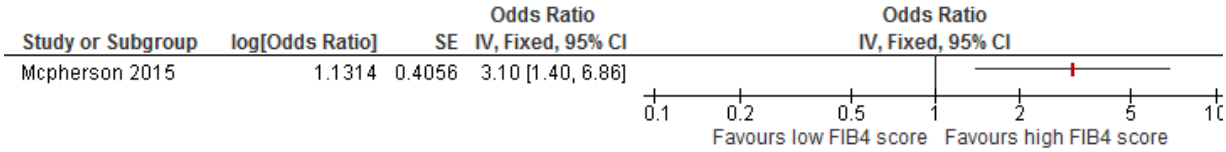


Adjusted in multivariate analysis using changes in BMI, ALT and waist circumference

Nb. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC centre practice.

2

Figure 140: FIB-4 score at follow up as a risk factor for fibrosis progression



Adjusted in multivariate analysis for platelet count, GGT (Gamma-glutamyl transpeptidase), AST/ALT ratio (alanine aminotransferase ratio/ Aspartate transaminase), FIB4 score (FIB4 age = [years] × AST [IU/L]/platelet count [expressed as platelets × 10^9/L] × (ALT$^{1/2}$[IU/L]) , NAFLD progression score (NAFLD score-=-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl)

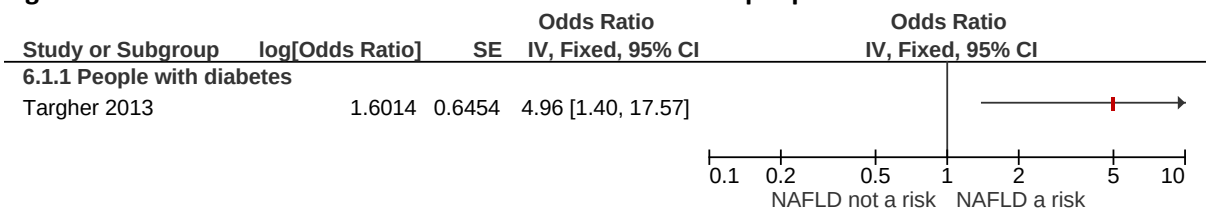
Nb. The GDG requested that the forest plots be titled with 'favouring' indicating a higher chance of fibrosis progression, rather than indicating less likely to have a negative outcome as is the normal NCGC centre practice.

3 # K.5 Extra-hepatic conditions

4 ## K.5.1 Cardiovascular disease

5 ### K.5.1.1 Atrial fibrillation

Figure 141: NAFLD as a risk factor for atrial fibrillation in people with diabetes



1K.5.1.2 Cardiovascular events

Figure 142: Hepatic steatosis as a risk factor for cardiovascular events

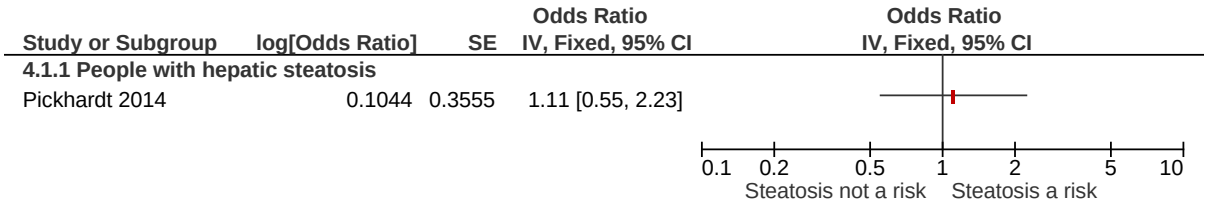


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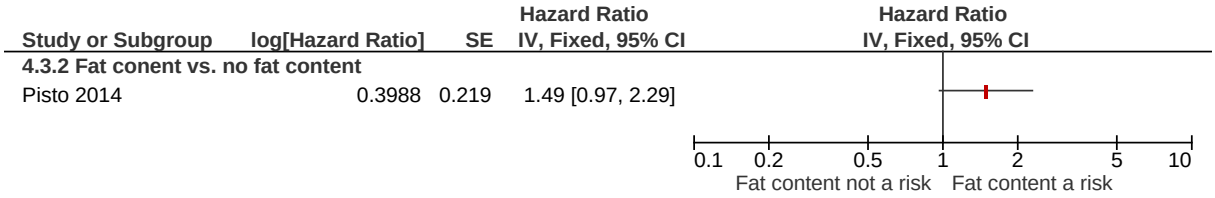
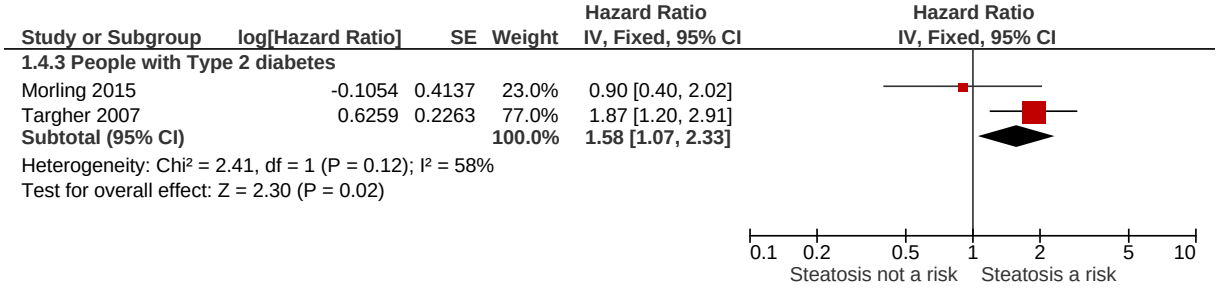
Figure 143: Fat content as a risk factor for cardiovascular events



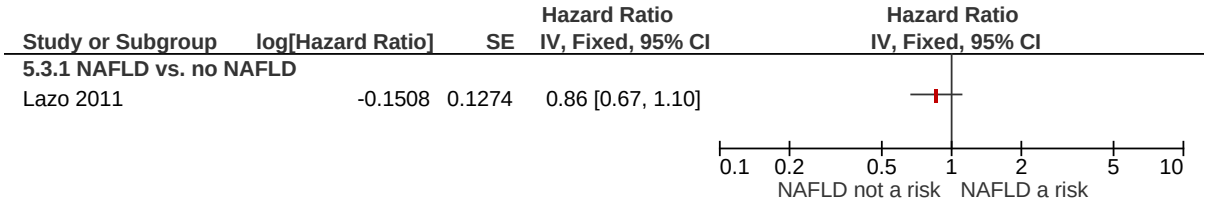
3

Figure 144: Hepatic steatosis as a risk factor for cardiovascular events in people with Type 2 diabetes



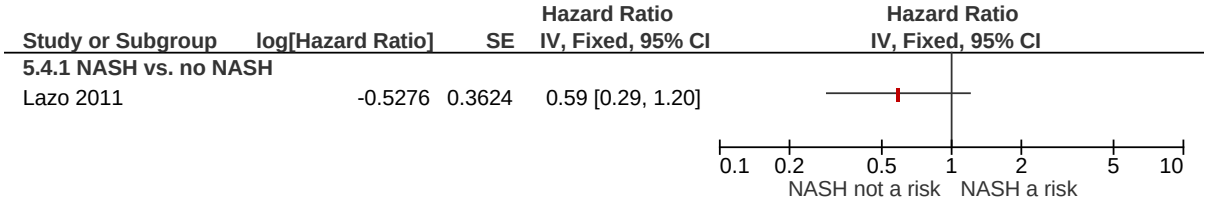
4K.5.1.3 Cardiovascular mortality

Figure 145: NAFLD as a risk factor for cardiovascular-related death



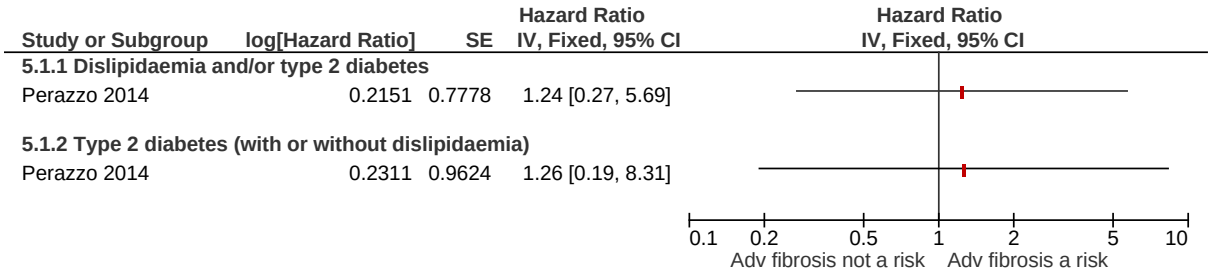
5

Figure 146: NASH as a risk factor for cardiovascular-related death



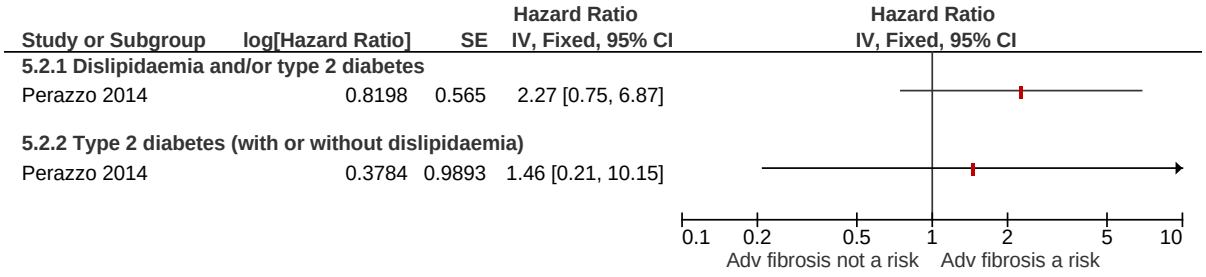
1

Figure 147: Advanced fibrosis as a risk factor for cardiovascular-related death in people with dyslipidaemia and/or type 2 diabetes



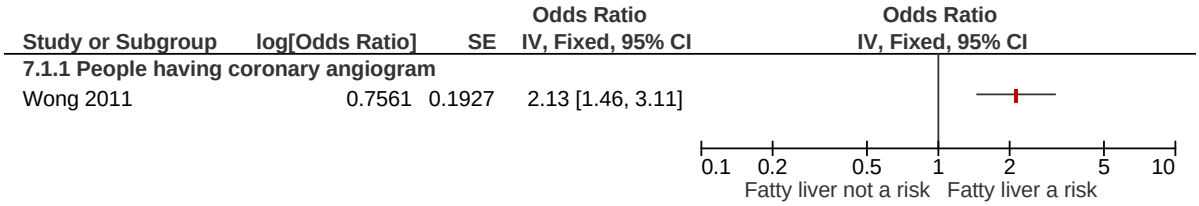
2

Figure 148: Severe steatosis as a risk factor for cardiovascular-related death in people with dyslipidaemia and/or type 2 diabetes



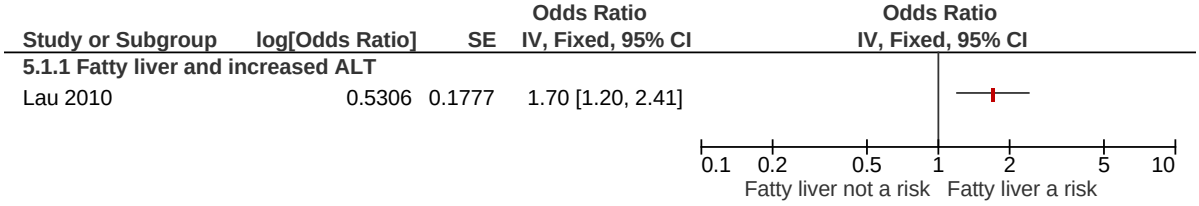
3K.5.1.4 Coronary artery disease

Figure 149: Fatty liver as a risk factor for coronary artery disease in people who have undergone coronary angiogram



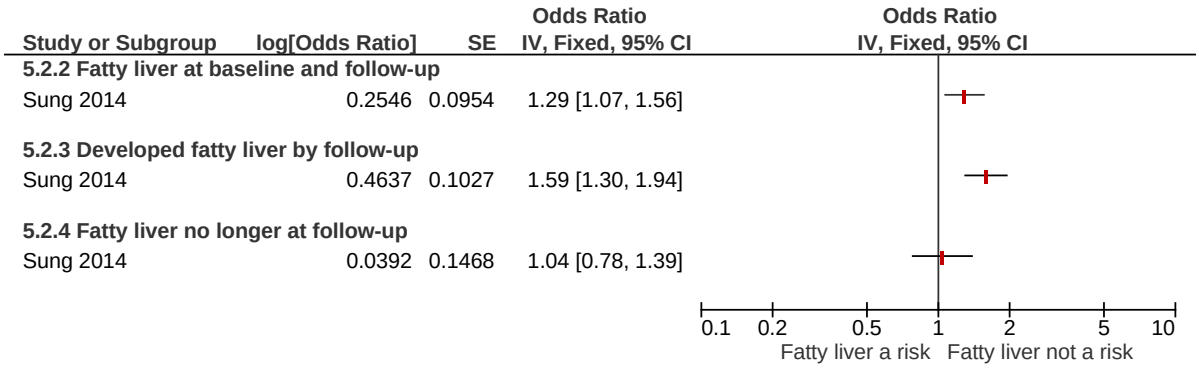
4K.5.1.5 Hypertension

Figure 150: Fatty liver + increased ALT as a risk factor for hypertension compared to no fatty liver and normal ALT



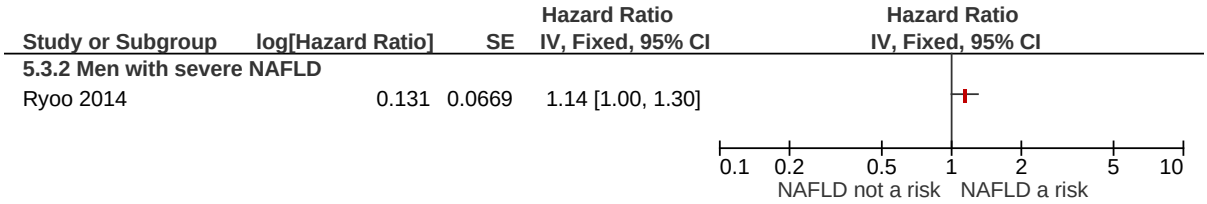
5

Figure 151: Fatty liver status over time as a risk factor for hypertension in comparison to those without fatty liver at baseline or follow-up



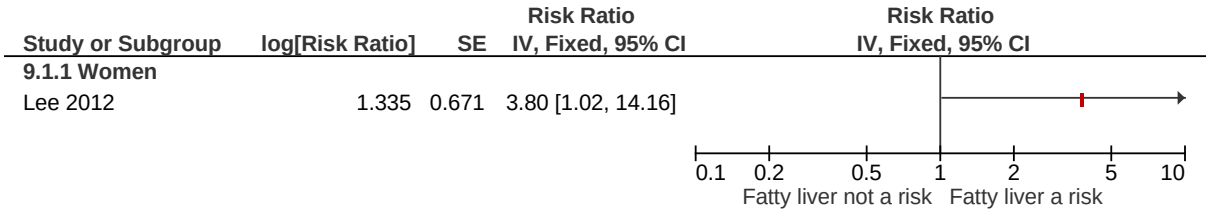
1

Figure 152: NAFLD as a risk factor for hypertension in men



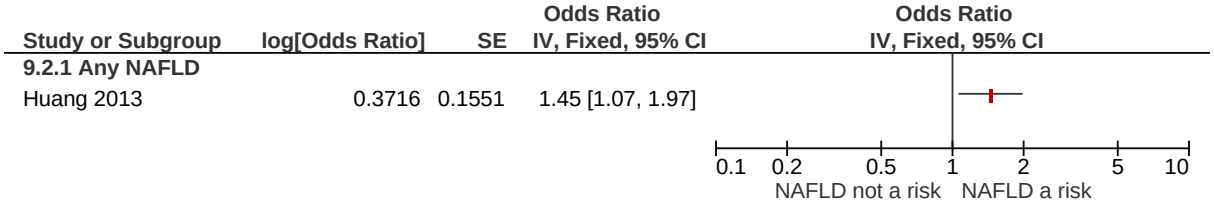
2 K.5.2 Colorectal cancer

Figure 153: Fatty liver as a risk factor for colorectal cancer in women



3

Figure 154: NAFLD as a risk factor for colorectal adenoma



K.5.3 Diabetes

Figure 155: NAFLD as a risk factor for diabetes

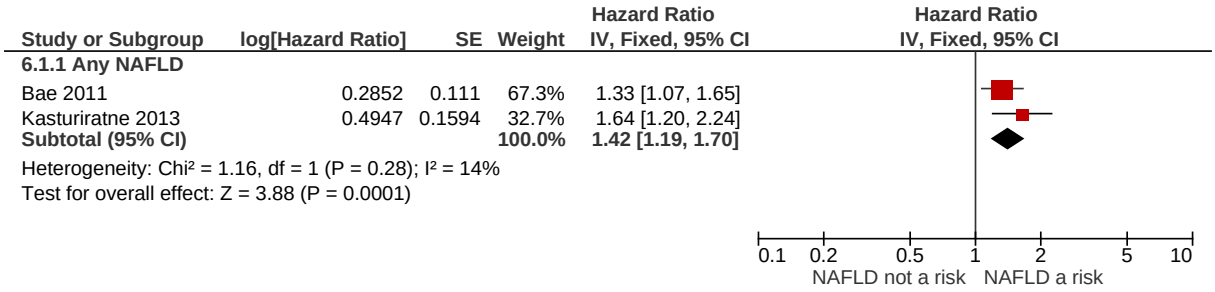


Figure 156: Fatty liver as a risk factor for diabetes

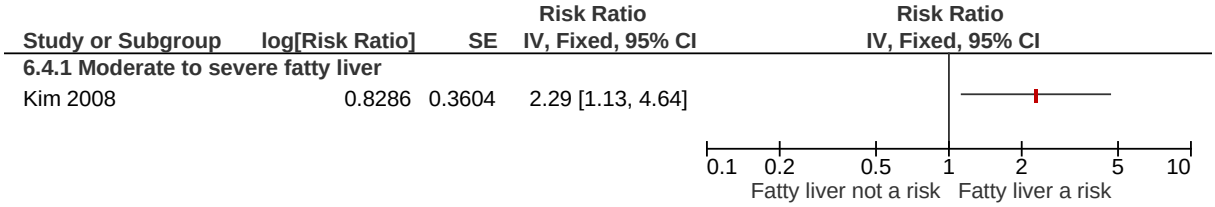


Figure 157: NAFLD as a risk factor for diabetes in men

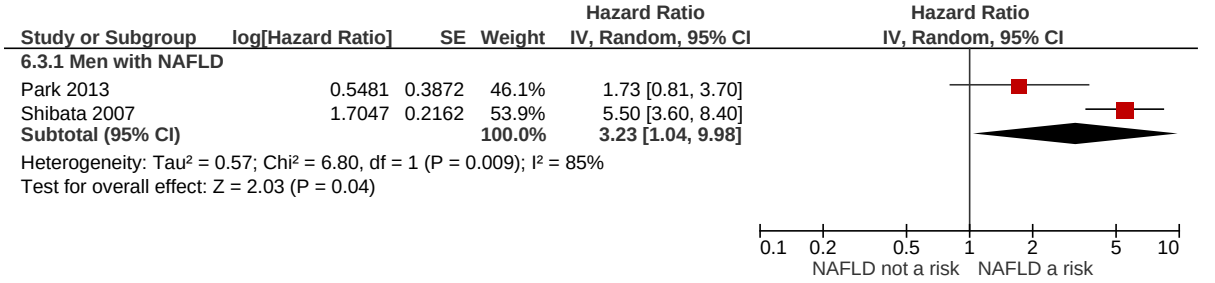


Figure 158: Fatty liver as a risk factor for diabetes according to gender

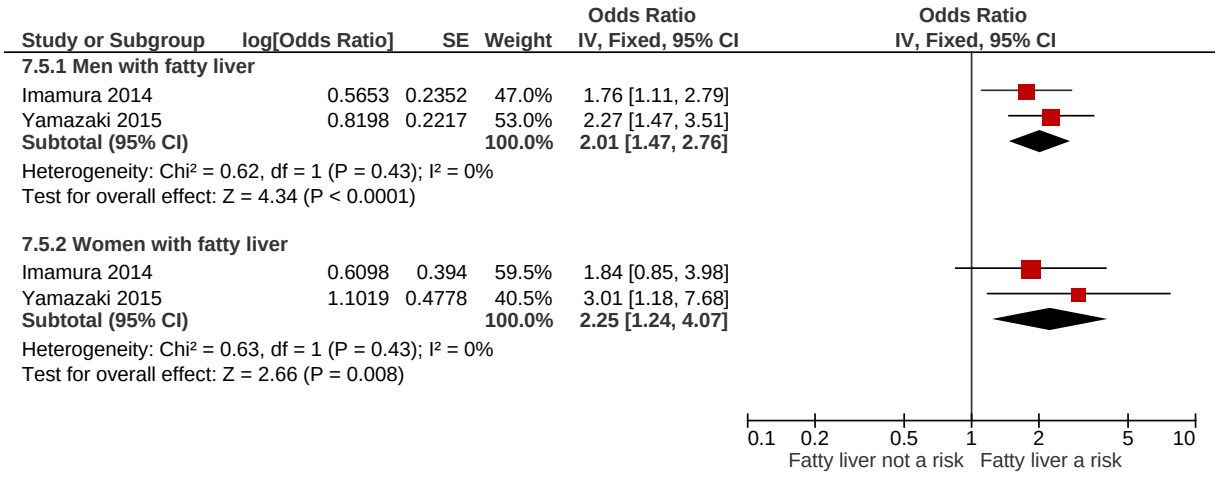
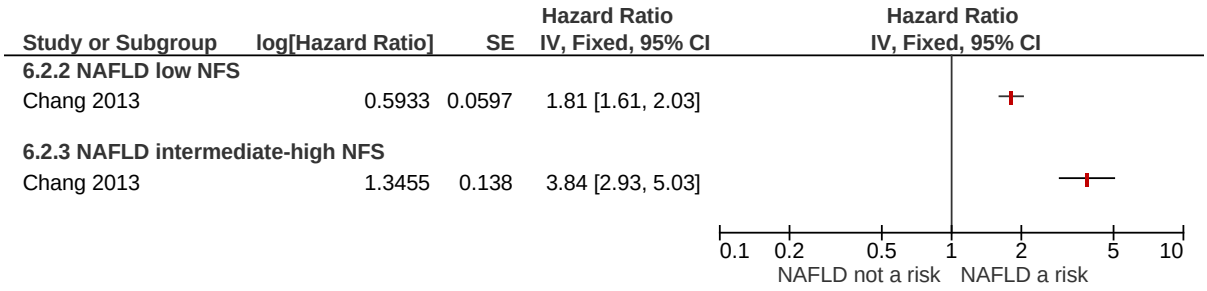
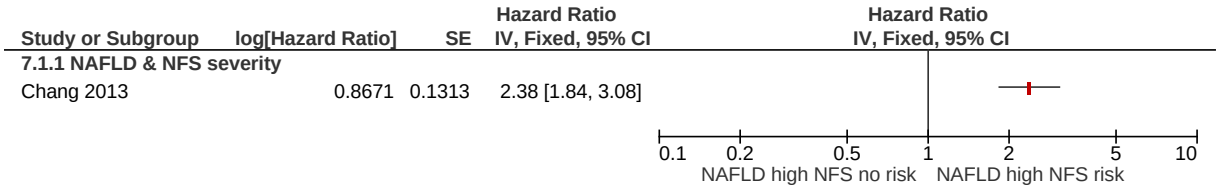


Figure 159: Severity of NAFLD and fibrosis score as a risk factor for diabetes in comparison with no NAFLD



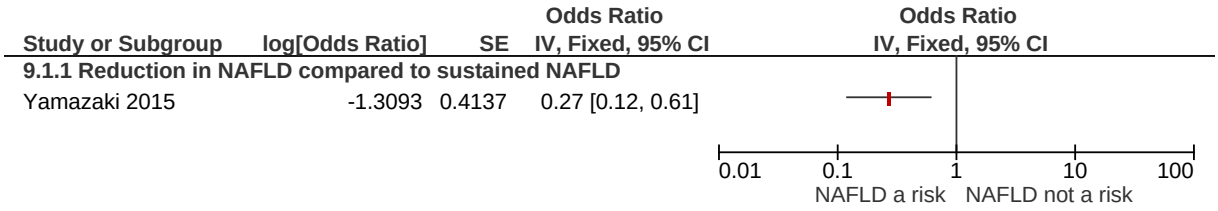
1

Figure 160: NAFLD and high fibrosis score as a risk factor for diabetes in comparison with NAFLD and low fibrosis score



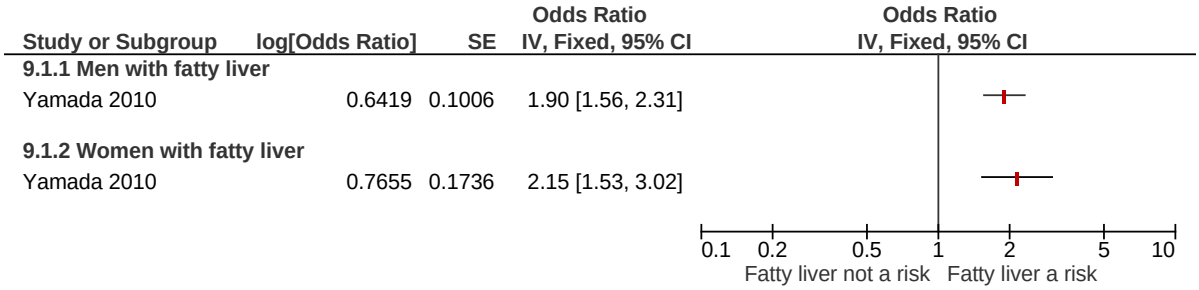
2

Figure 161: Improvement in NAFLD as a risk factor for diabetes in comparison with sustained NAFLD



3

Figure 162: Fatty liver as a risk factor for diabetes or impaired fasting glucose



K.5.4 Chronic kidney disease

Figure 163: NAFLD as a risk factor for chronic kidney disease in men

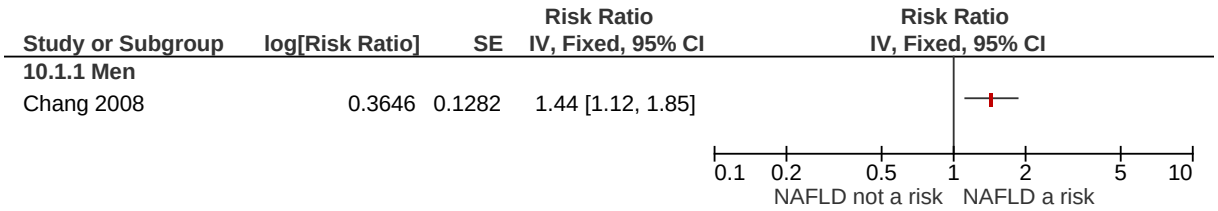


Figure 164: NAFLD as a risk factor for chronic kidney disease in people with type 2 diabetes

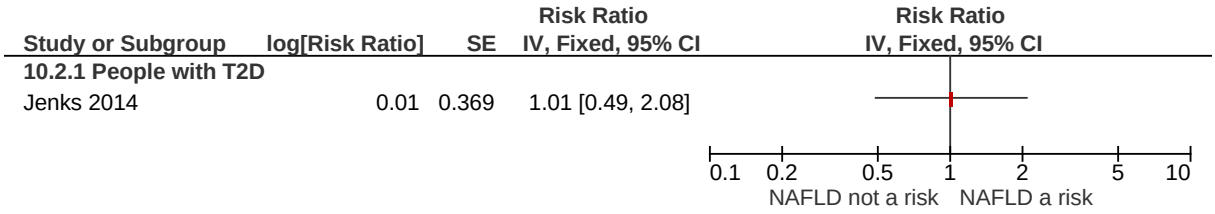
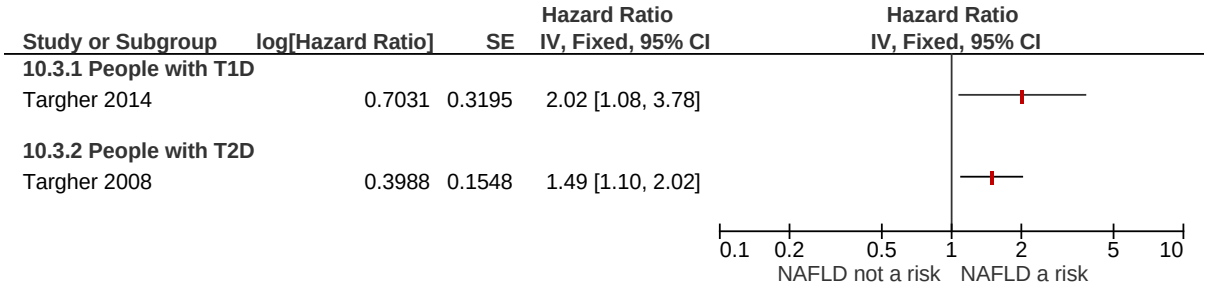


Figure 165: NAFLD as a risk factor for chronic kidney disease in people with either type 1 or type 2 diabetes



K.6 Dietary modification and supplements

K.6.1 Probiotics verses placebo or usual care: RCT

Figure 166: NAFLD progression; MRS hepatic triglyceride content (adults), ≥3 months to <12 months

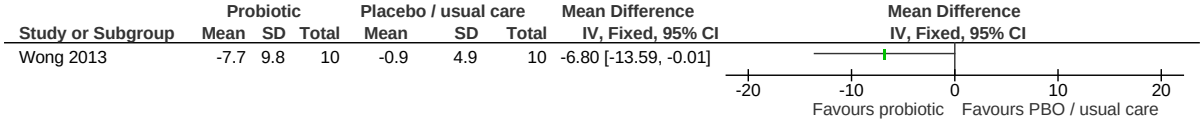
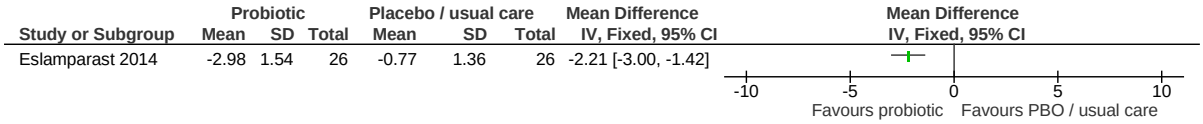
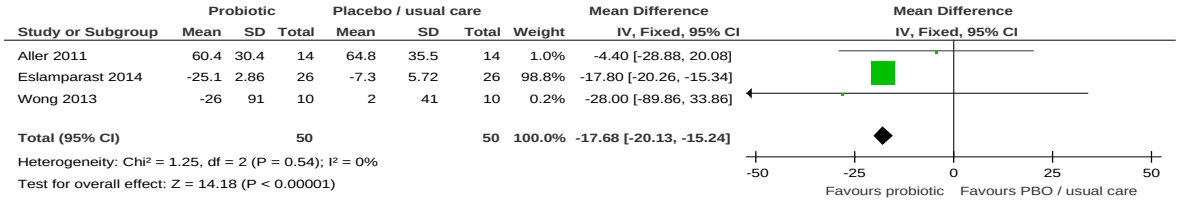


Figure 167: NAFLD progression; transient elastography fibrosis score (adults), ≥3 months to <12 months



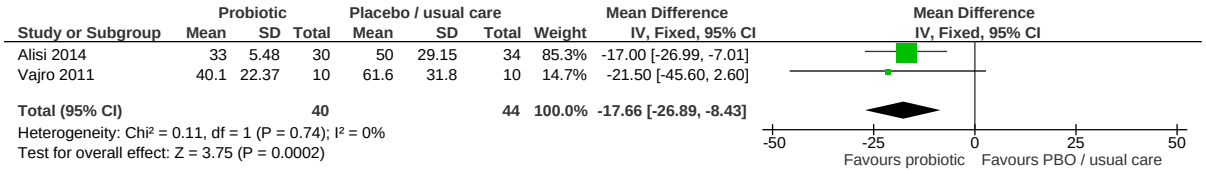
1

Figure 168: ALT (U/l) (adults), ≥3 months to <12 months



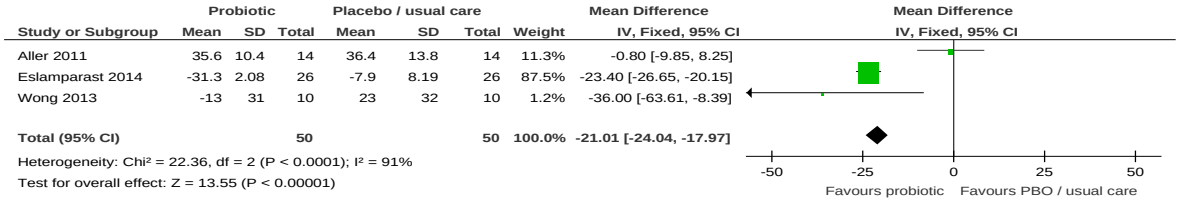
2

Figure 169: ALT (U/l) (children / young adults), ≥3 months to <12 months



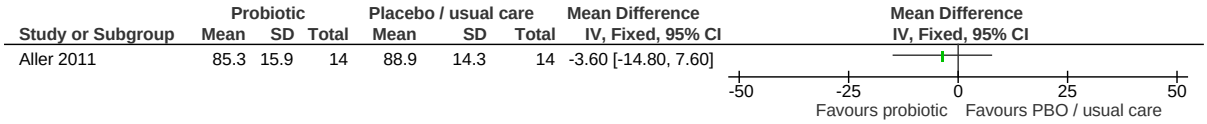
3

Figure 170: AST (U/l) (adults), ≥3 months to <12 months



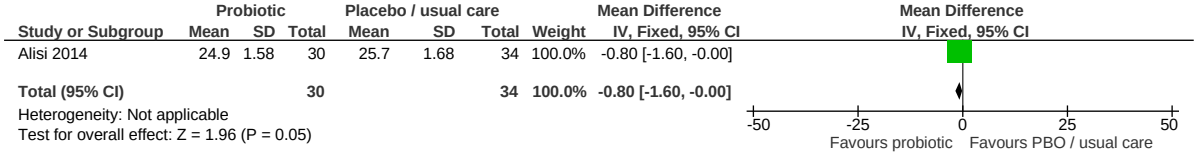
4

Figure 171: Weight (kg) adults, ≥3 months to <12 months



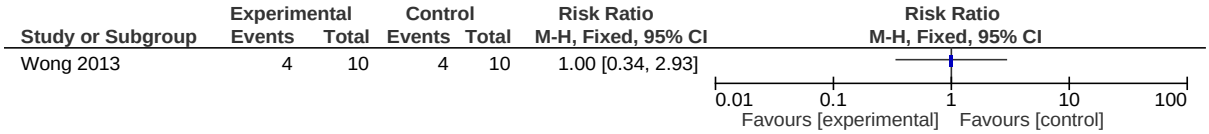
5

Figure 172: Weight loss (BMI at end of study) (children / young people), ≥3 months to <12 months



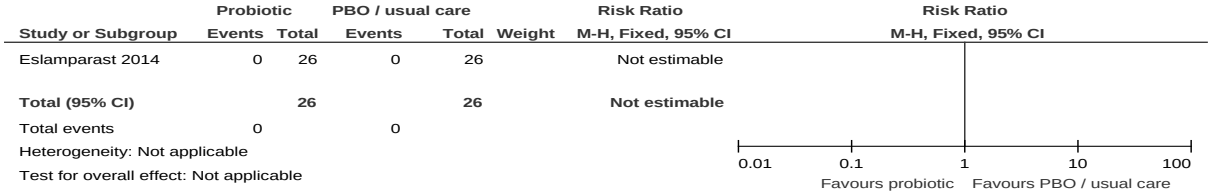
6

Figure 173: Any adverse event (adults), ≥3 months to <12 months



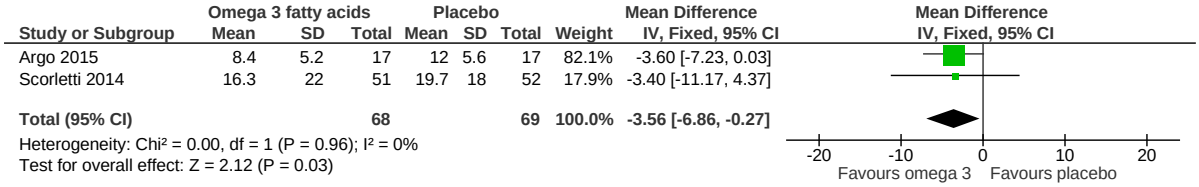
7

Figure 174: Serious adverse event (adults), ≥3 months to <12 months



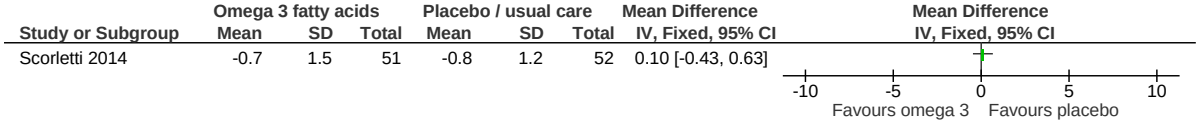
1 K.6.2 Omega-3 fatty acids verses placebo or usual care: RCTs

Figure 175: NAFLD progression; liver fat (%) determined by MRS, (adults), ≥12 months



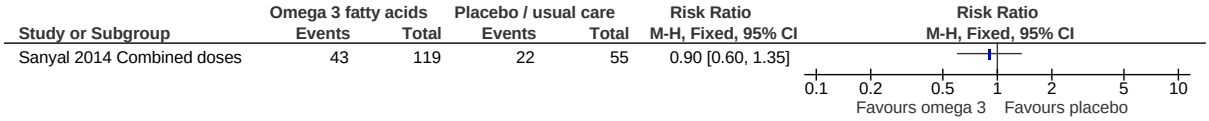
2

Figure 176: NAFLD progression; NAFLD fibrosis score, (adults), ≥12 months



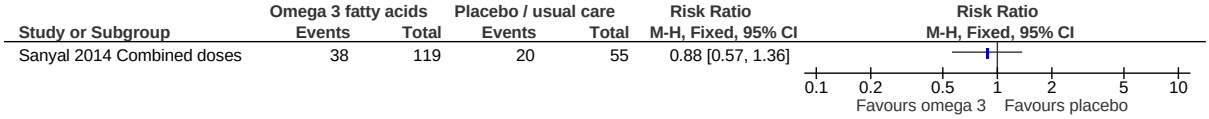
3

Figure 177: NAFLD progression; composite of NAS ≤3/fibrosis unchanged and/or NAS decrease ≥2/ fibrosis unchanged (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months



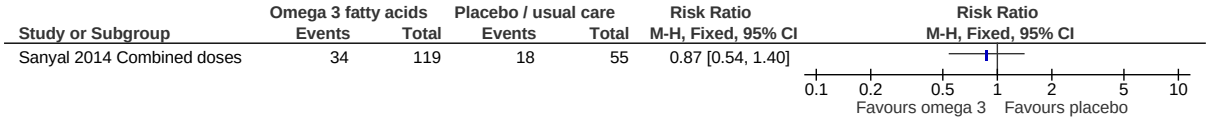
4

Figure 178: NAFLD progression; NAS ≤3/fibrosis unchanged, combined doses (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months



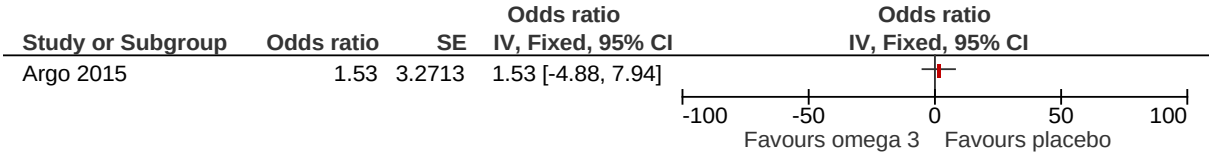
5

Figure 179: NAFLD progression; NAS decrease ≥2/ fibrosis unchanged, combined doses (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months



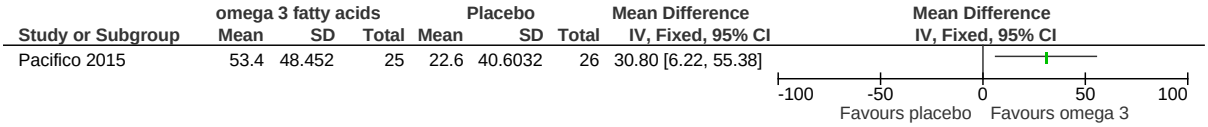
6

Figure 180: NAFLD progression; NAS, (adults), ≥12 months



1

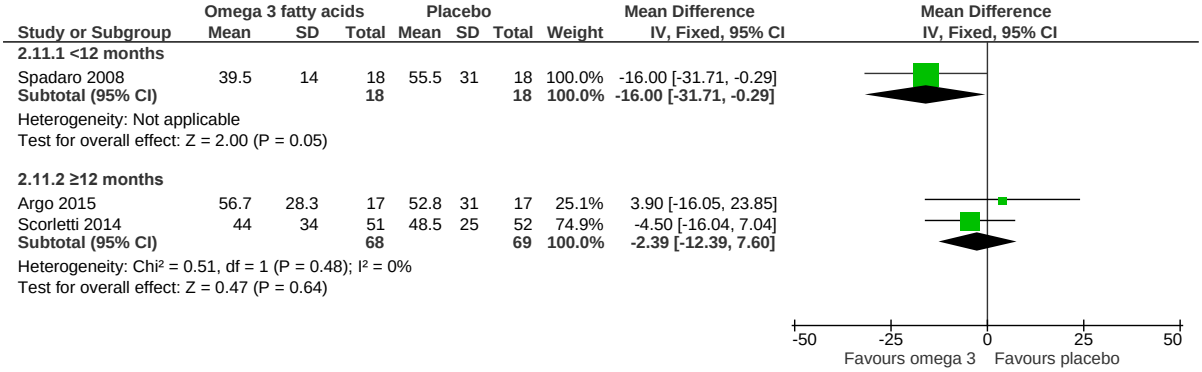
Figure 181: NAFLD progression; % reduction in MRI hepatic fat fraction, (children and young people) ≥3 months to <12 months



NB study reports odds ratio adjusted for weight change, age and baseline NAS value. SE is calculated by NCGC. Data not analysed in GRADE

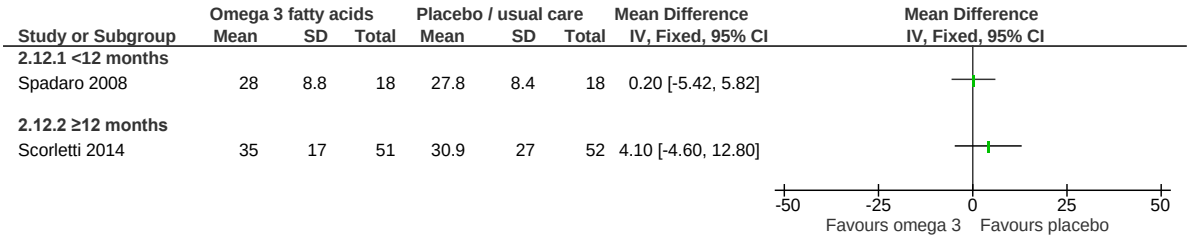
2

Figure 182: ALT (U/l), (adults)



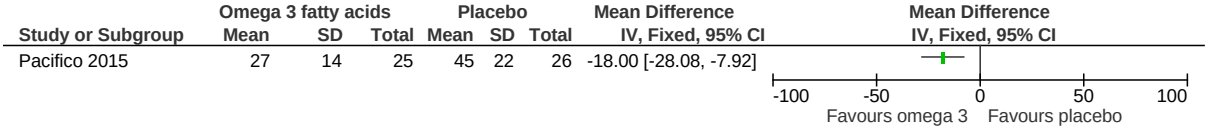
3

Figure 183: AST (U/l) (adults)



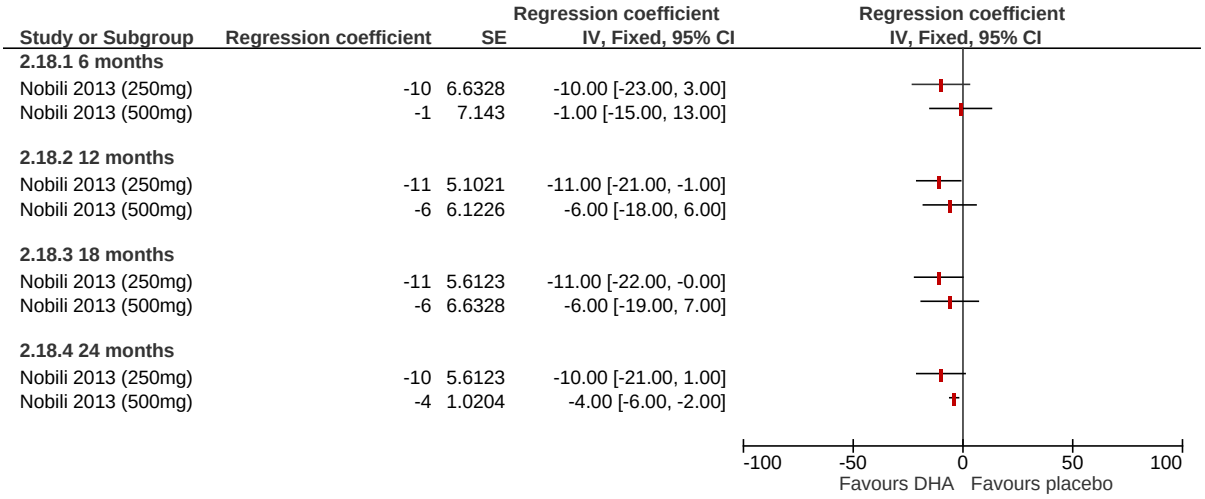
4

Figure 184: ALT (U/l) (children and young people), ≥3 months to <12 months



5

Figure 185: ALT (U/l) (children and young people), ≥12 months



NB data only reported as regression co-efficient and confidence intervals – not analysed in GRADE

Figure 186: Weight (kg) (adults), ≥12 months

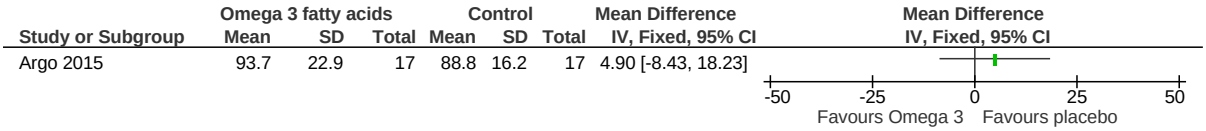


Figure 187: Weight loss ≥5% (children and young people), 6 months

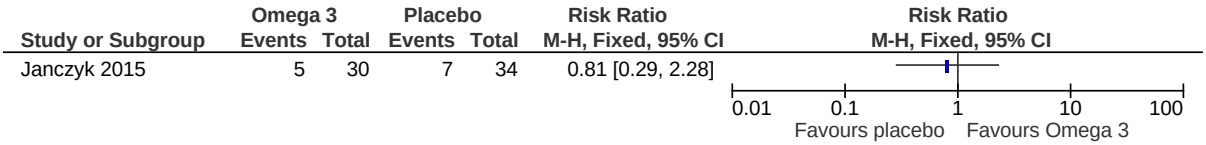


Figure 188: Final BMI levels (children and young people), 6 months

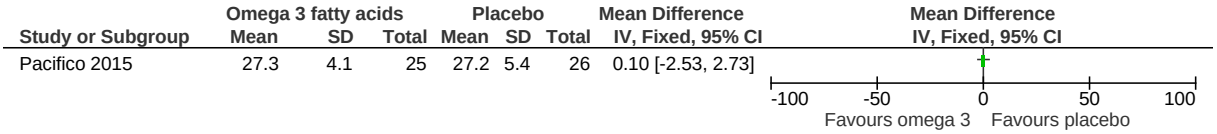


Figure 189: BMI reduction ≥5% (children and young people), 6 months

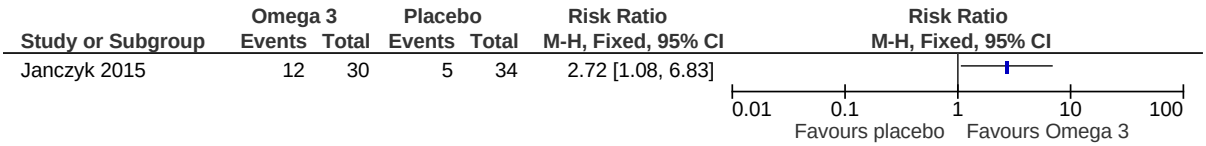
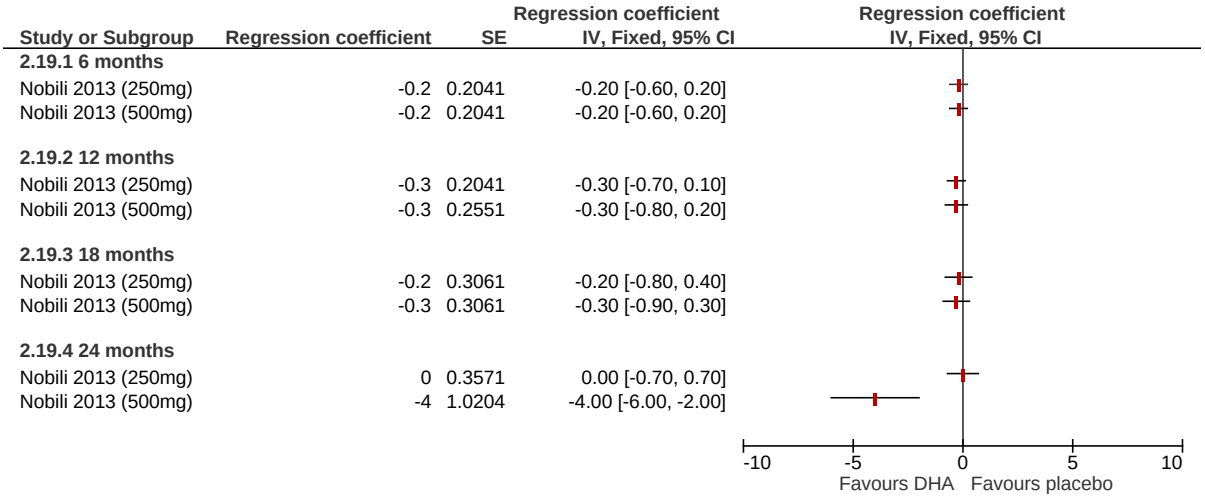


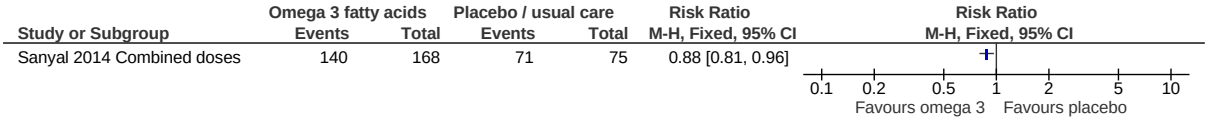
Figure 190: BMI (kg/m^2) (children and young people) ≥12 months



NB data only reported as regression co-efficient and confidence intervals – not analysed in GRADE

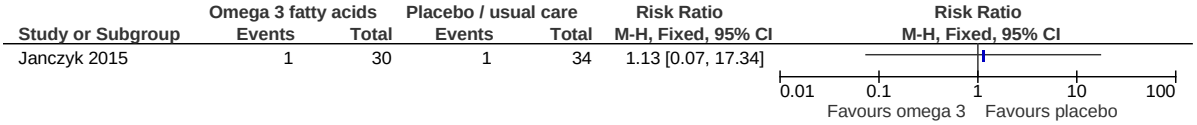
1

Figure 191: Any adverse event (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months



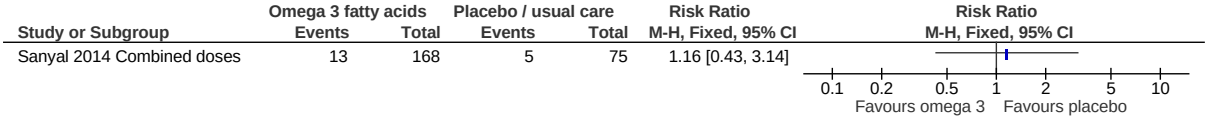
2

Figure 192: Any adverse event (children and young people) Mild abdominal discomfort 6 months



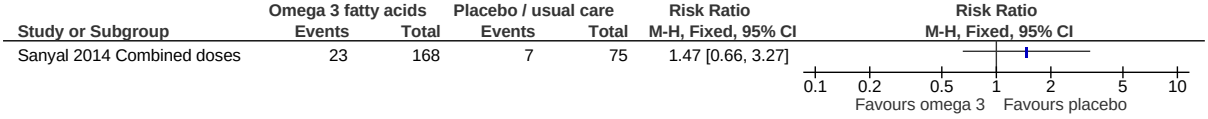
3

Figure 193: Serious adverse event (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months



4

Figure 194: Severe adverse event (adults), combined omega 3 doses (1800 mg/day and 2700 mg/day), ≥12 months



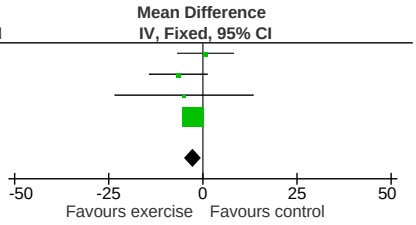
1 K.7 Exercise interventions

2 K.7.1 Exercise versus control

Figure 195: NAFLD progression; MRS intrahepatic lipid CH_2-water or intrahepatic triglyceride (%) (adults), ≥3 months to <12 months

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hallsworth 2011 RCT	12.2	9	11	11.5	7.4	8	8.9%	0.70 [-6.69, 8.09]
Pugh 2013 RCT	-13	5.4765	6	-6.5	7.1467	5	8.3%	-6.50 [-14.14, 1.14]
Sullivan 2012 RCT	17	8.2916	11	22	22.0454	6	1.4%	-5.00 [-23.31, 13.31]
Thoma 2013 RCT	7.8	2.4	15	10.4	3.9	13	81.3%	-2.60 [-5.04, -0.16]
Total (95% CI)			**43**			**32**	**100.0%**	**-2.67 [-4.87, -0.46]**

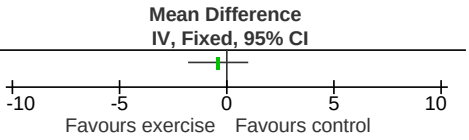
Heterogeneity: Chi² = 1.83, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)



3

Figure 196: NAFLD progression; liver biopsy NAS (range 0 to 8) (adults), ≥3 months to <12 months

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Eckert 2013 RCT	2.9	1.5	9	3.3	1.6	11	-0.40 [-1.76, 0.96]

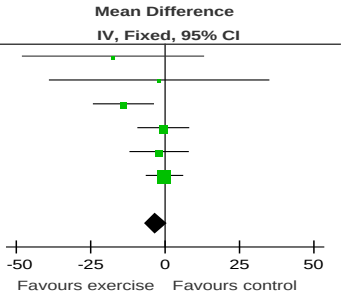


4

Figure 197: ALT levels (U/l) (adults), ≥3 months to <12 months

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Eckert 2013 RCT	-21.8	30.6	9	-4.3	38.7	11	1.7%	-17.50 [-47.88, 12.88]
Hallsworth 2011 RCT	59.6	39	11	61.6	41.4	8	1.2%	-2.00 [-38.80, 34.80]
Pugh 2013 RCT	29	6.6703	6	43	9.6645	5	15.7%	-14.00 [-24.01, -3.99]
Sullivan 2012 RCT	39.3	7.4	12	39.9	9.2	6	21.9%	-0.60 [-9.07, 7.87]
Thoma 2013 RCT	33	15	12	35	8	11	16.7%	-2.00 [-11.71, 7.71]
Zelber-Sagi 2014 RCT	-5.3	9.65	33	-5.1	14.43	31	42.9%	-0.20 [-6.25, 5.85]
Total (95% CI)			**83**			**72**	**100.0%**	**-3.07 [-7.03, 0.90]**

Heterogeneity: Chi² = 6.68, df = 5 (P = 0.25); I² = 25%
Test for overall effect: Z = 1.52 (P = 0.13)

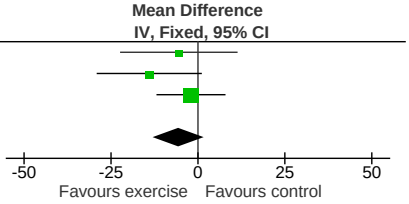


5

Figure 198: AST levels (U/l) (adults), ≥3 months to <12 months

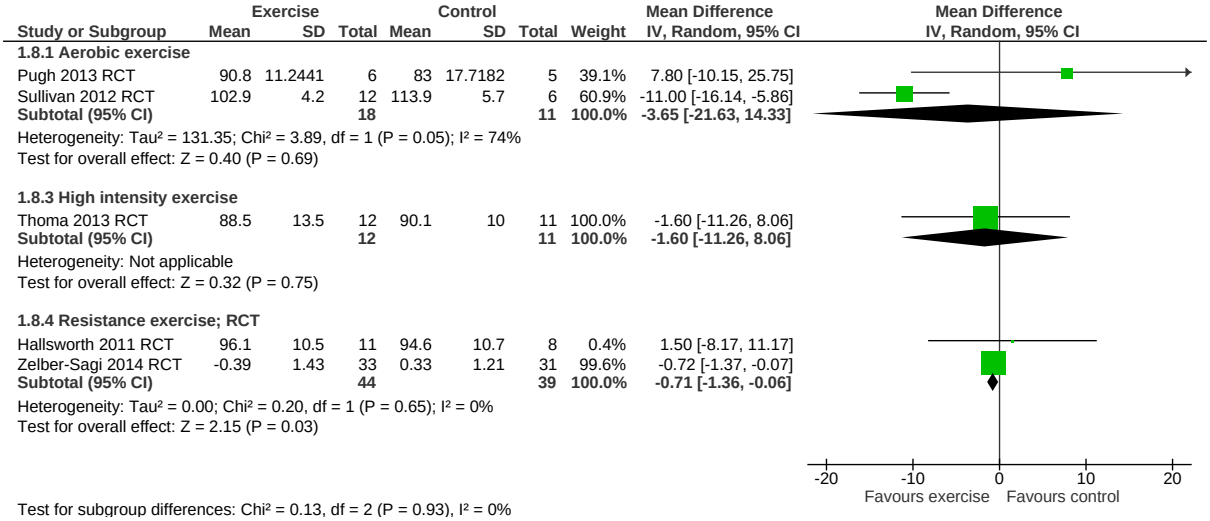
Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Eckert 2013 RCT	-8.4	10.4	9	-2.9	25.8	11	19.2%	-5.50 [-22.19, 11.19]
Pugh 2013 RCT	29	5.7174	6	43	16.1992	5	24.1%	-14.00 [-28.92, 0.92]
Thoma 2013 RCT	33	15	12	35	8	11	56.7%	-2.00 [-11.71, 7.71]
Total (95% CI)			**27**			**27**	**100.0%**	**-5.56 [-12.88, 1.76]**

Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)



6

Figure 199: Weight (kg) (adults), ≥3 months to <12 months

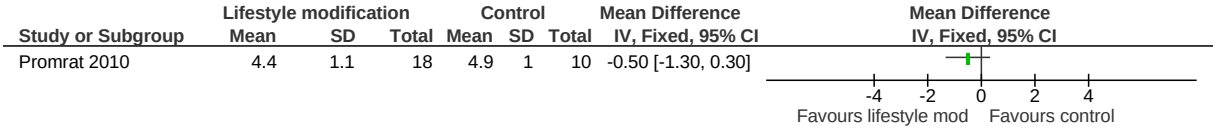


1 K.8 Lifestyle modification

2 K.8.1 Lifestyle modification (any diet plus exercise plus behavioural modification) versus control 3 (usual care) (RCTs)

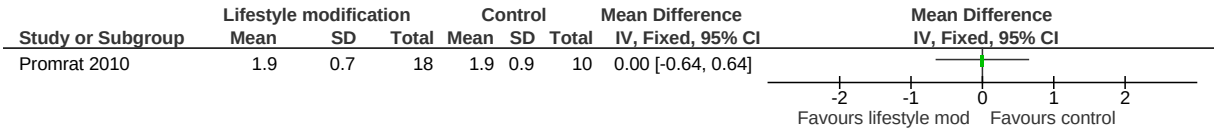
4K.8.1.1 <12 months

Figure 200: NAS (0-8, final value)



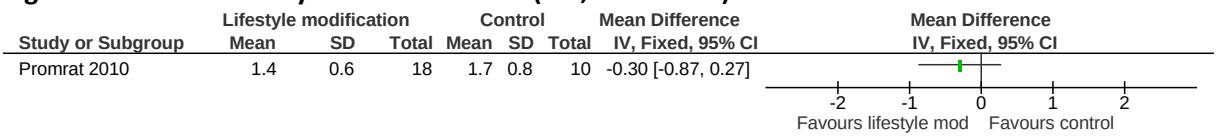
5

Figure 201: Fat (0-3, final value)



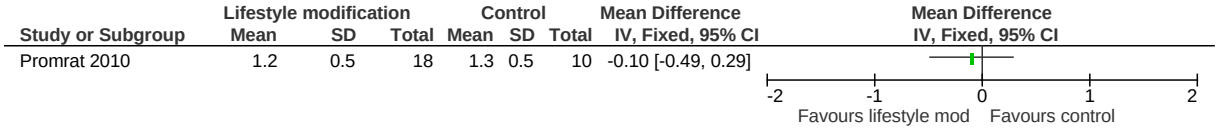
6

Figure 202: Parenchymal inflammation (0-3, final value)



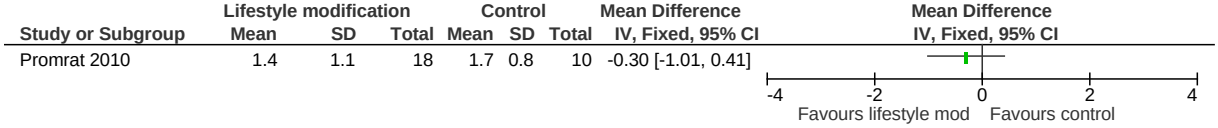
7

Figure 203: Ballooning injury (0-2, final value)



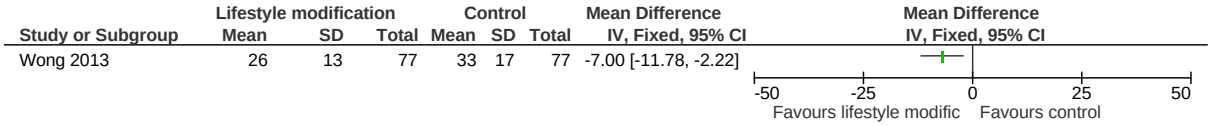
1

Figure 204: Fibrosis (0-4, final values)



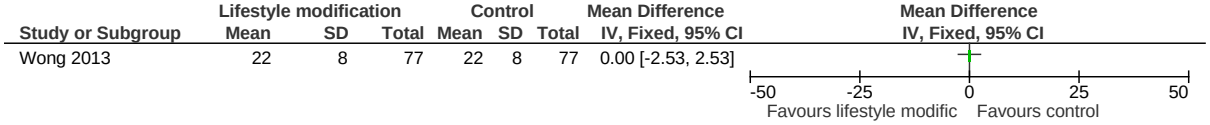
2K.8.1.2 ≥12 months

Figure 205: ALT levels (U/l, final values)



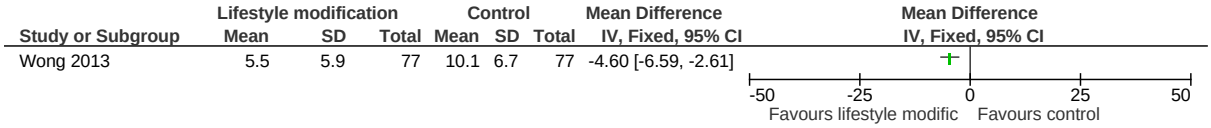
3

Figure 206: AST levels (U/l, final values)



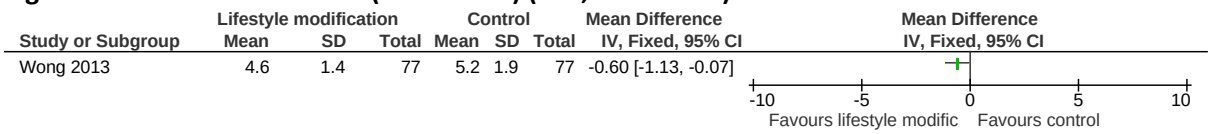
4

Figure 207: Intrahepatic triglyceride (^{1}H-MRS) (%, final value)



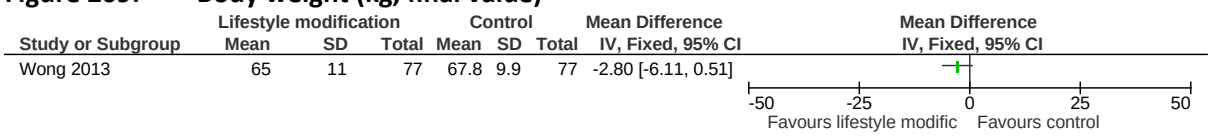
5

Figure 208: Liver stiffness (ultrasound) (kPa, final value)



6

Figure 209: Body weight (kg, final value)



K.8.2 Lifestyle modification (any diet plus exercise plus behavioural modification) versus control (usual care) (cohort study) ≥12 months

Figure 210: ALT (U/l, final values)

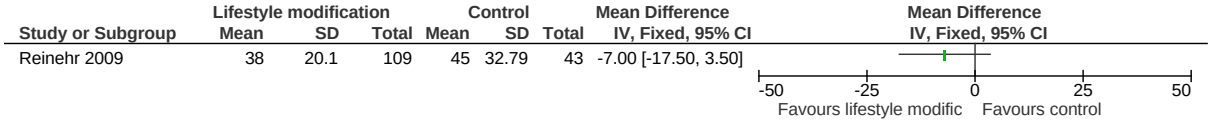


Figure 211: AST (U/l, final values)

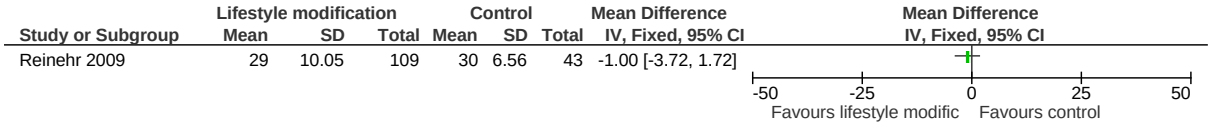
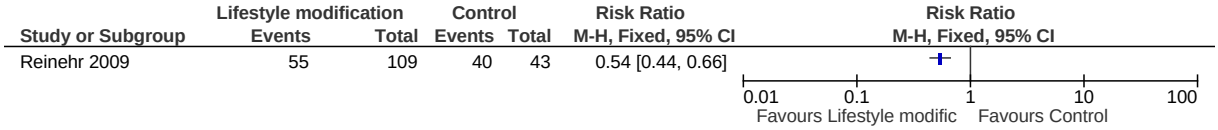
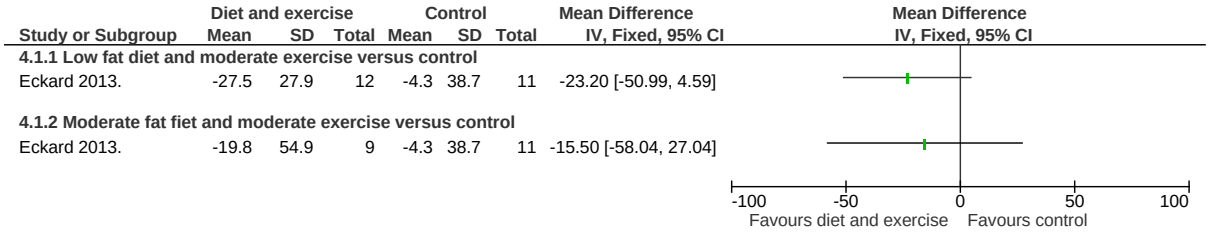


Figure 212: NAFLD (prevalence (ultrasound)



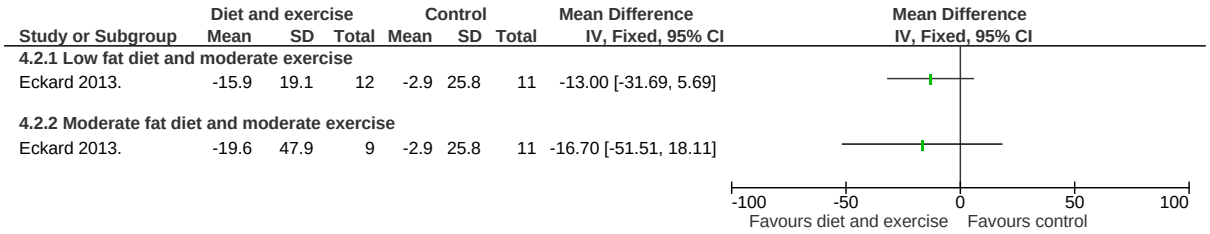
K.8.3 Diet and exercise versus control (usual care) (RCTs) >12 months

Figure 213: ALT (U/l, change scores)



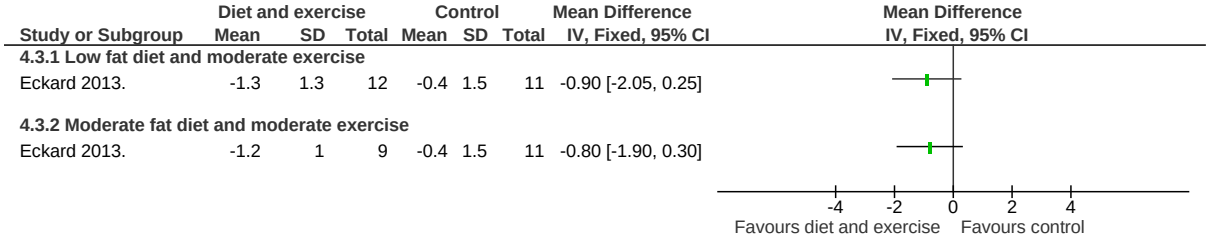
NOTE: double counting of the control group

Figure 214: AST (U/l, change score)



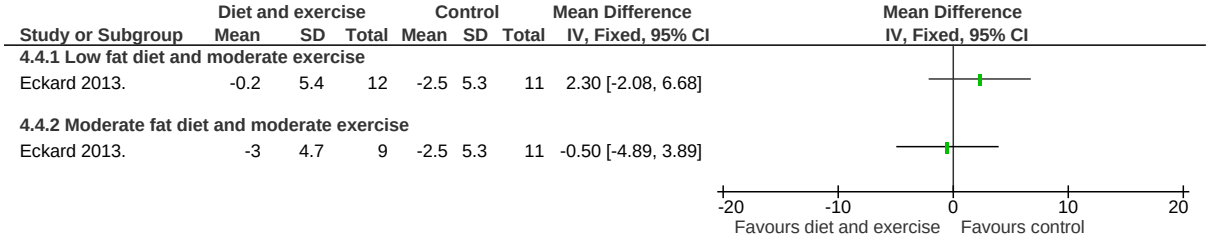
NOTE: double counting of the control group

Figure 215: NAFLD activity score (0–8, change score)



NOTE: double counting of the control group

Figure 216: Body weight (kg, change score)



NOTE: double counting of the control group

K.8.4 Diet and exercise versus control (Chen 2008: no control details, Ueno 1997: usual care) (cohort studies) <12 months

Figure 217: ALT (U/l, final values)

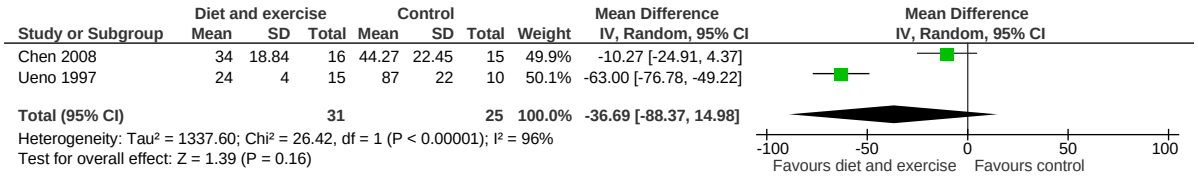


Figure 218: AST (U/l, final values)

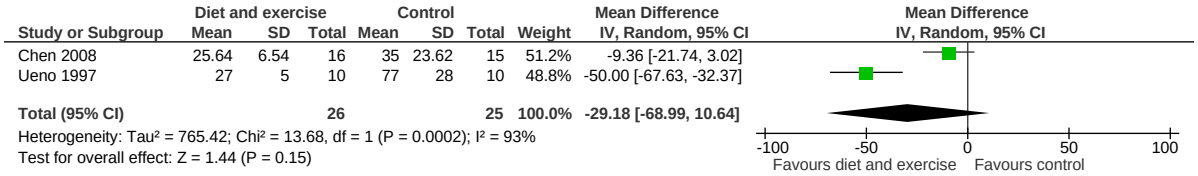


Figure 219: NAFLD progression with fibroscan (0–3 severity scale, final values)

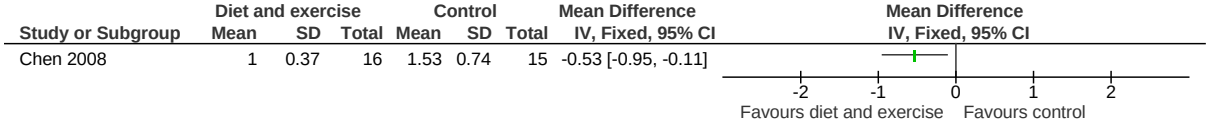
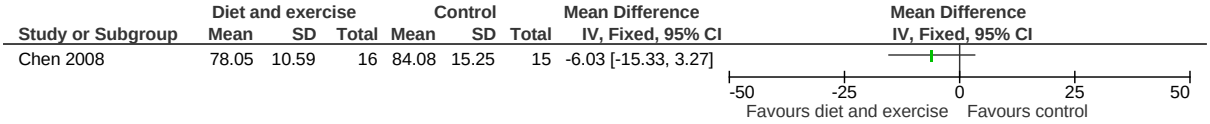
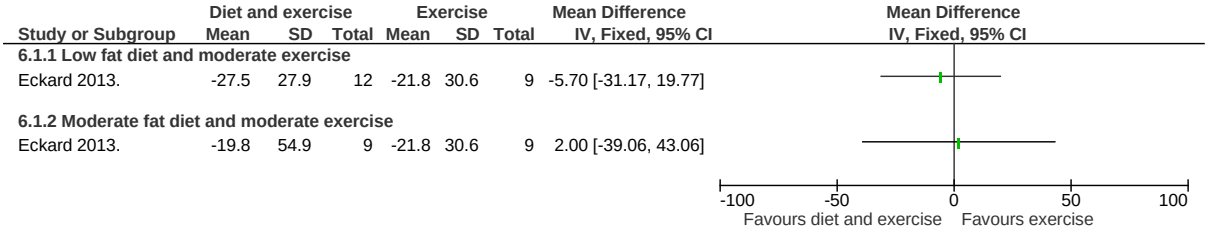


Figure 220: Body weight (kg, final values)



1 K.8.5 Diet and exercise versus exercise (RCTs) <12 months

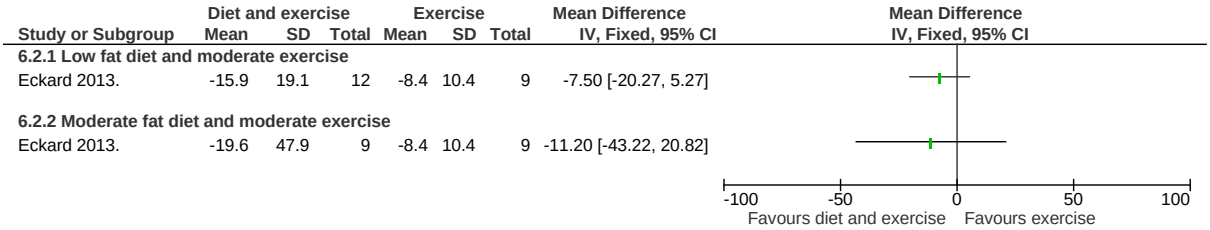
Figure 221: ALT (U/l, change score)



NOTE: double counting of the control group

2

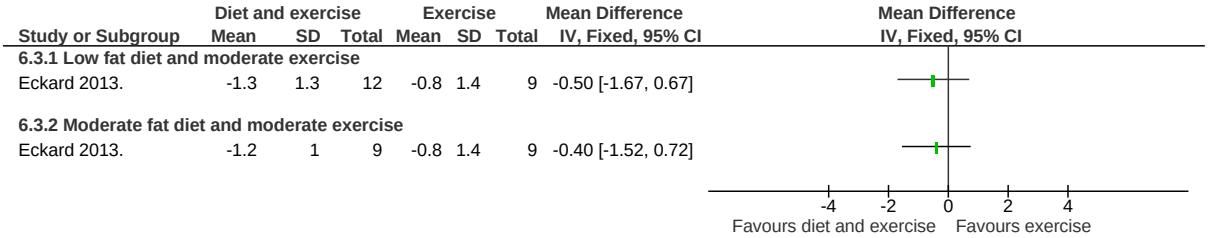
Figure 222: AST (U/l, change score)



NOTE: double counting of the control group

3

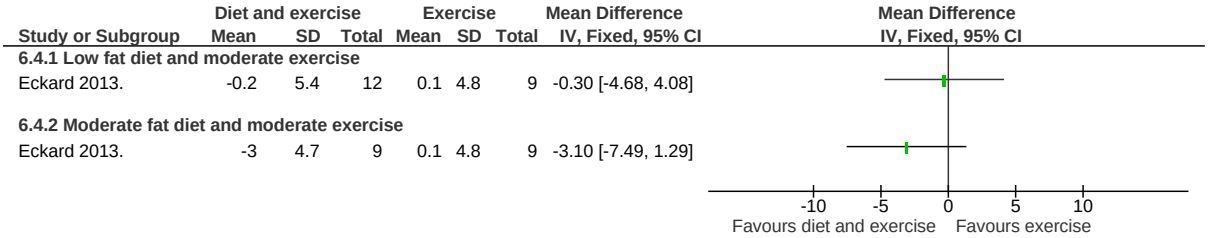
Figure 223: NAFLD activity score (0–8, change score)



NOTE: double counting of the control group

4

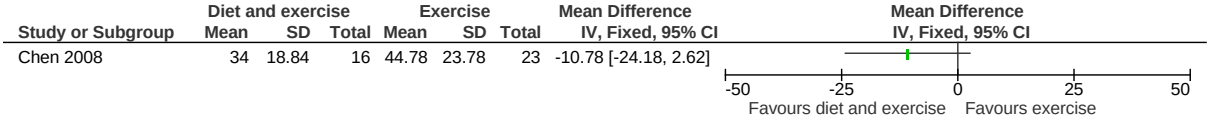
Figure 224: Body weight (kg, change score)



NOTE: double counting of the control group

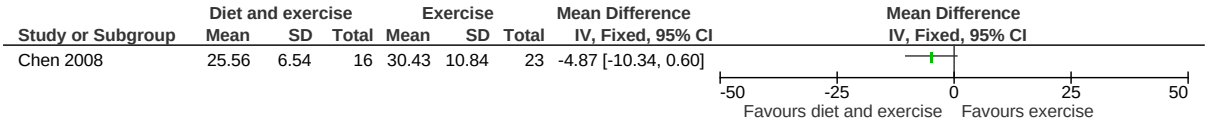
1 K.8.6 Diet and exercise versus exercise (cohort study) <12 months

Figure 225: ALT (U/l, final value)



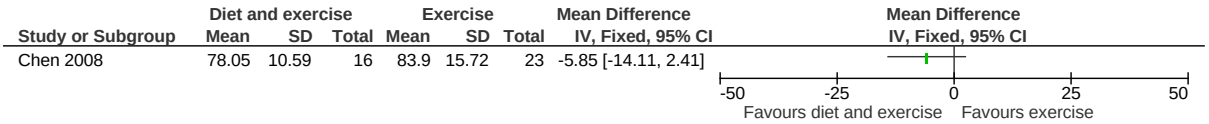
2

Figure 226: AST (U/l, final value)



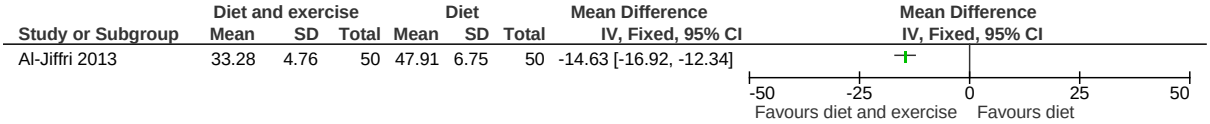
3

Figure 227: Body weight (kg, final value)



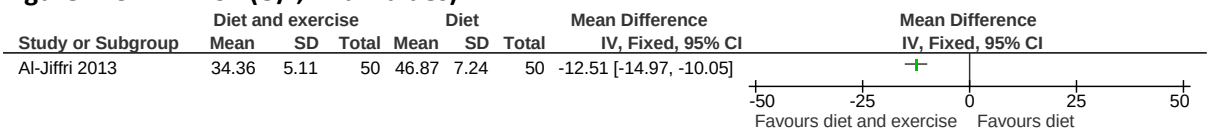
4 K.8.7 Diet and exercise versus diet (RCTs) <12 months

Figure 228: ALT (U/l, final values)



5

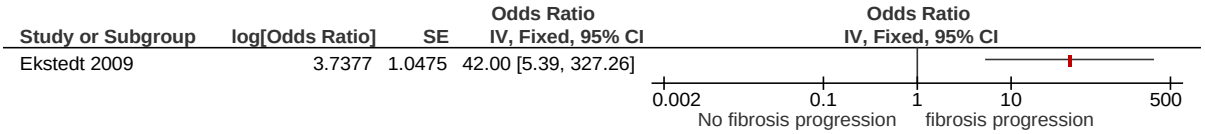
Figure 229: AST (U/l, final values)



6 # K.9 Alcohol advice

7 K.9.1 Fibrosis progression

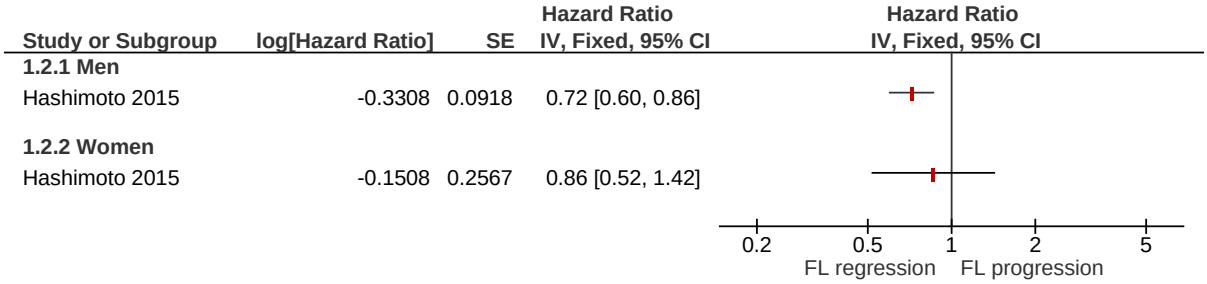
Figure 230: Heavy episodic drinking >1 a month (>60 g males/48 g females ethanol in one episode)



(a) Multivariate analysis included: age, gender, BMI, diabetes, weight gain, IR HOMA (insulin resistance according to homeostasis model assessment), fibrosis stage at baseline

1 K.9.2 Presence of fatty liver disease

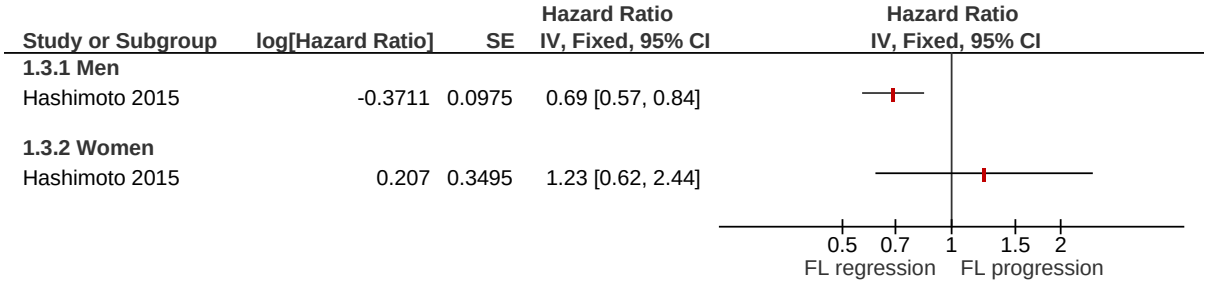
Figure 231: Light drinker (40-140 g ethanol/week)



Multivariate analysis included: age, BMI, smoker status, and regular exercise (defined as >1 episode of any type of sport undertaken per week

2

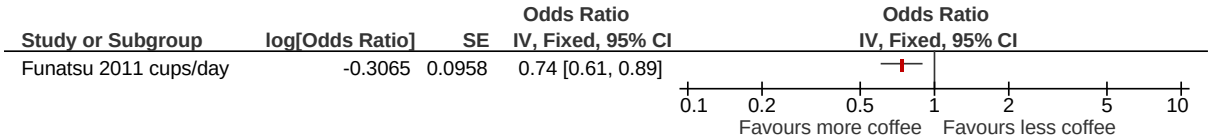
Figure 232: Moderate drinker (140-280g ethanol/week)



(a) Multivariate analysis included: age, BMI, smoker status, and regular exercise (defined as >1 episode of any type of sport undertaken per week)

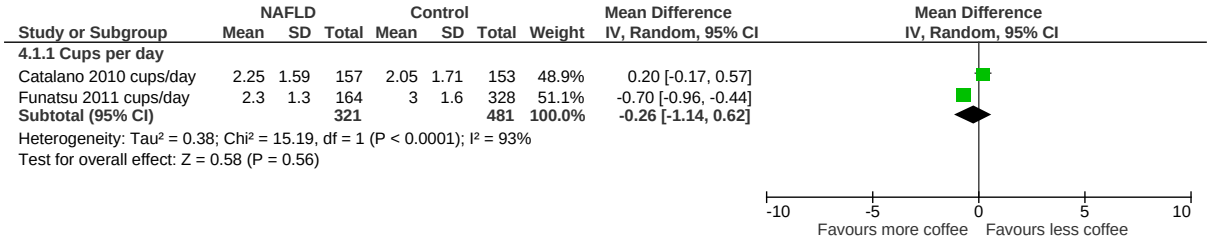
3 K.10 Caffeine advice

Figure 233: Presence of NAFLD determined by ultrasound



4

Figure 234: Coffee consumption in people with NAFLD vs controls

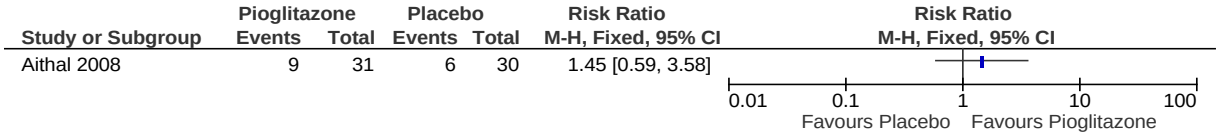


1K.11 Pharmacological interventions

2K.11.1 Pioglitazone versus placebo for adults with NAFLD

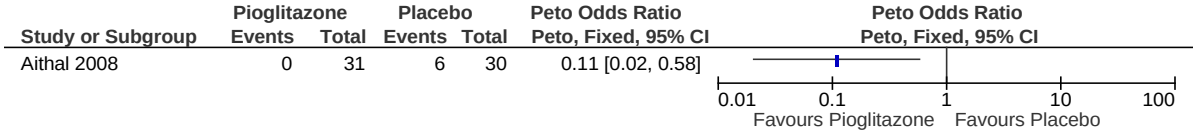
3K.11.1.1 Progression of NAFLD (CRITICAL)

Figure 235: Decrease in fibrosis [>12 months]



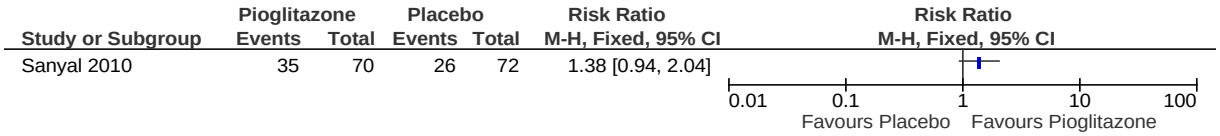
4

Figure 236: Increase in fibrosis [> 12 months]



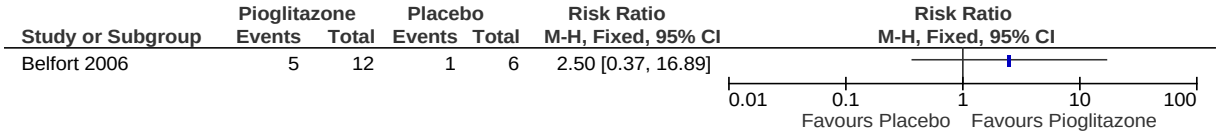
5

Figure 237: Improvement in fibrosis [>12 months]



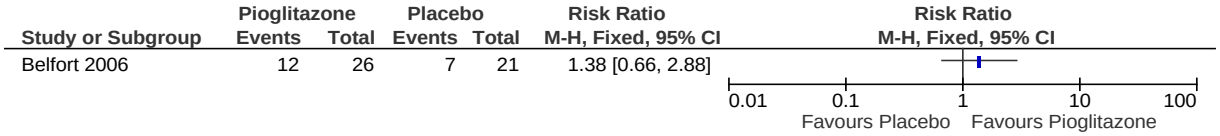
6

Figure 238: Reduction in fibrosis score of ≥2 [≥3 months to <12 months]



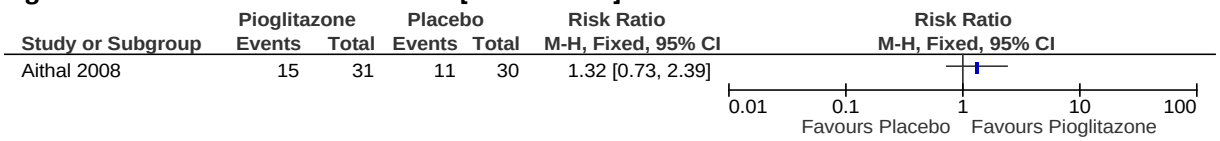
7

Figure 239: Reduction in fibrosis [≥3 months to <12 months]



8

Figure 240: Decrease in steatosis [>12 months]



9

Figure 241: Increase in steatosis score [> 12 months]

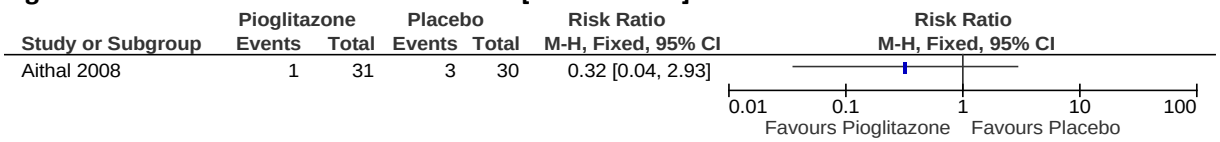


Figure 242: Improvement in steatosis [>12 months]

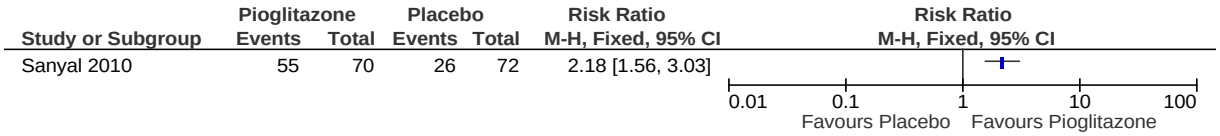


Figure 243: Reduction in steatosis score of ≥2 [≥3 months to <12 months]

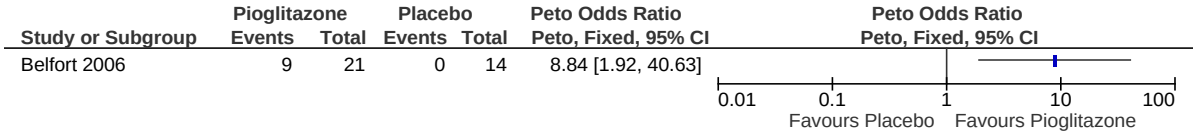


Figure 244: Decrease in hepatocellular injury [>12 months]

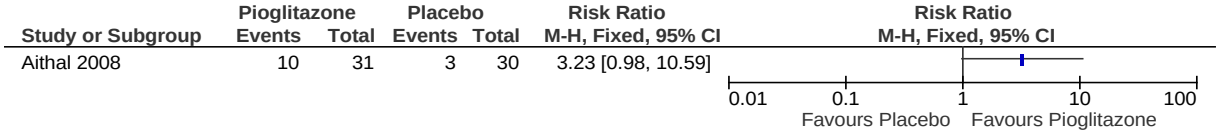


Figure 245: Increase in hepatocellular injury [>12 months]

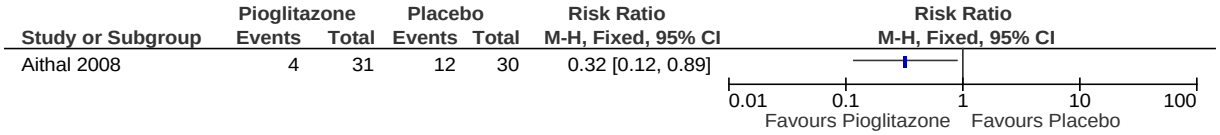


Figure 246: Improvement in hepatocellular ballooning [>12 months]

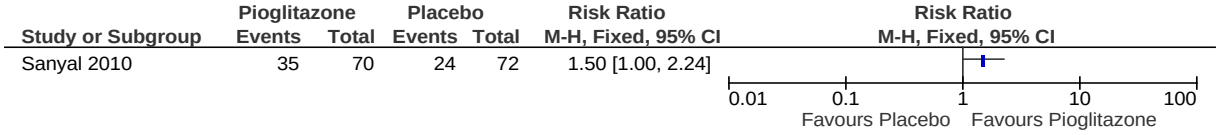
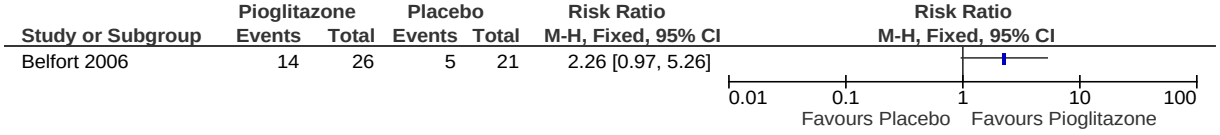
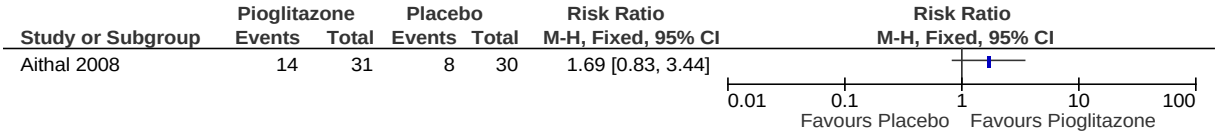


Figure 247: Improvement in ballooning necrosis [≥3 months to <12 months]



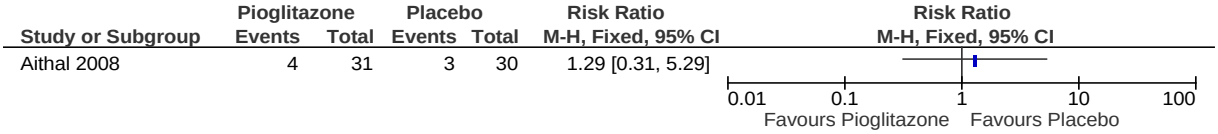
1

Figure 248: Decrease in lobular inflammation [>12 months]



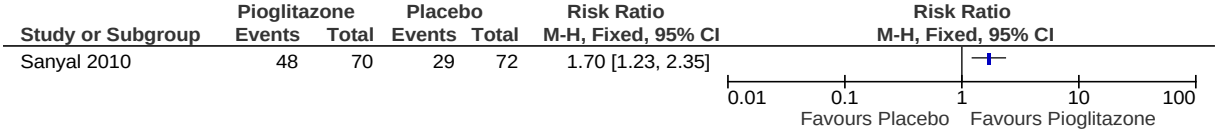
2

Figure 249: Increase in lobular inflammation [>12 months]



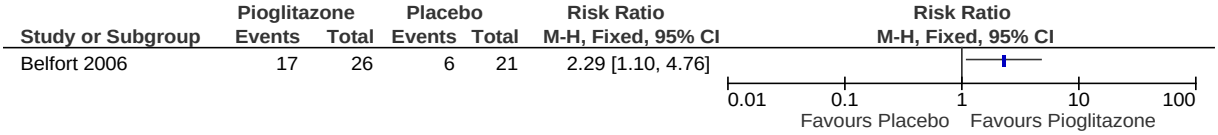
3

Figure 250: Improvement in lobular inflammation [>12 months]



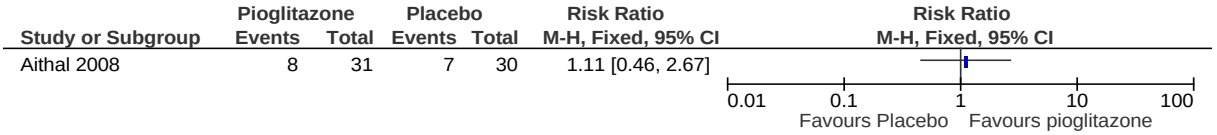
4

Figure 251: Improvement in lobular inflammation [≥3 months to <12 months]



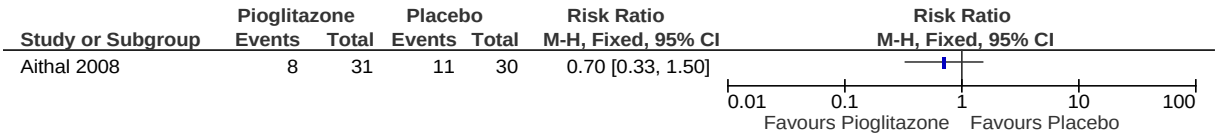
5

Figure 252: Decrease in portal inflammation [>12 months]



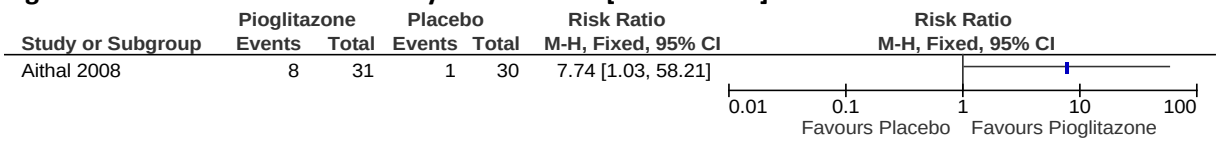
6

Figure 253: Increase in portal inflammation [>12 months]



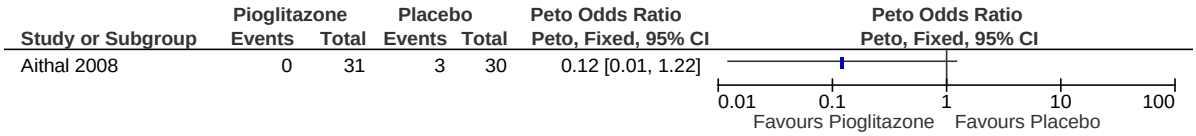
7

Figure 254: Decrease in Mallory-Denk bodies [>12 months]



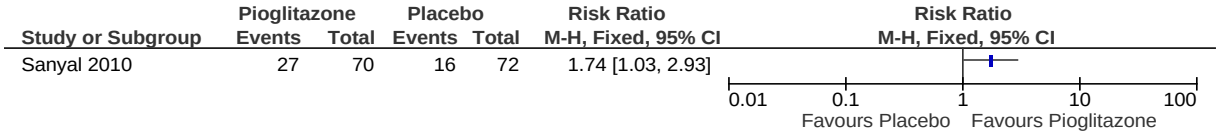
1

Figure 255: Increase in Mallory-Denk bodies [>12 months]



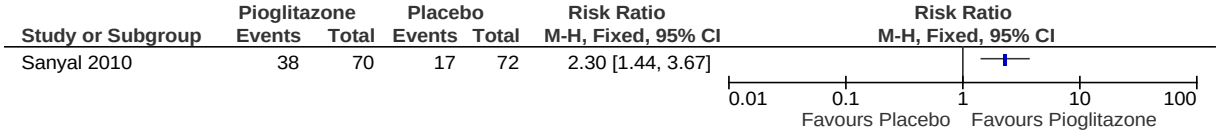
2

Figure 256: Improvement in histologic features of the liver [>12 months]



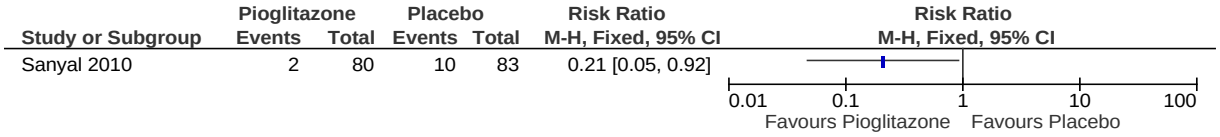
3

Figure 257: Resolution of definite NASH [>12 months]



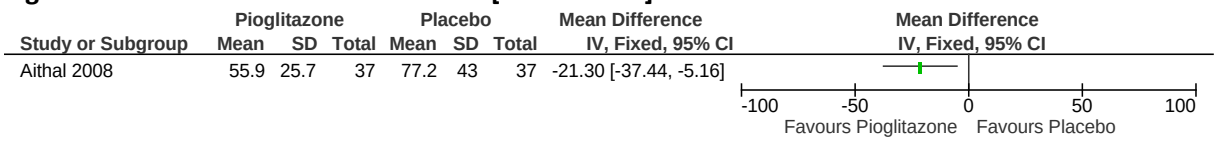
4.11.1.2 Serious adverse events (CRITICAL)

Figure 258: Severe adverse events [>12 months]



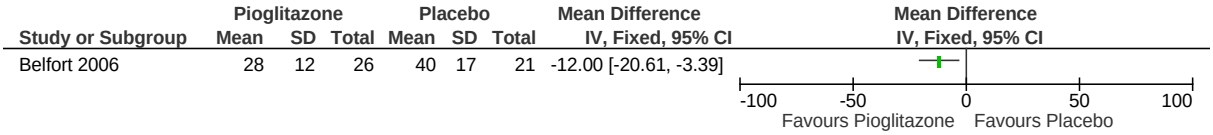
5.11.1.3 Liver function tests (IMPORTANT)

Figure 259: ALT levels – final values [>12 months]



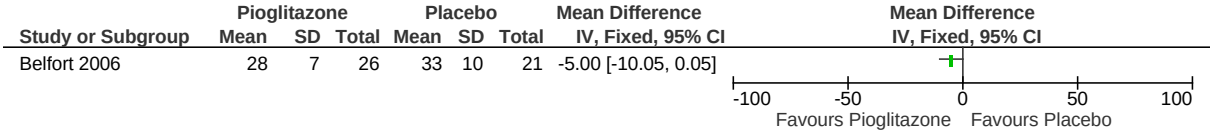
1

Figure 260: ALT levels – final values [≥3 months to <12 months]



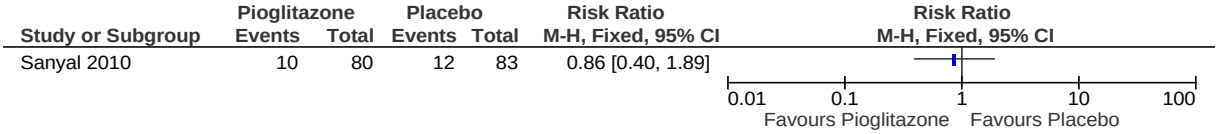
2

Figure 261: AST levels – final values [≥3 months to <12 months]



8.11.1.4 Adverse events (IMPORTANT)

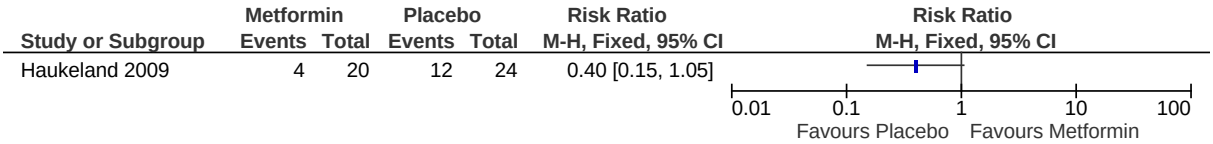
Figure 262: Adverse cardiovascular events [>12 months]



4.11.2 Metformin versus placebo for adults with NAFLD

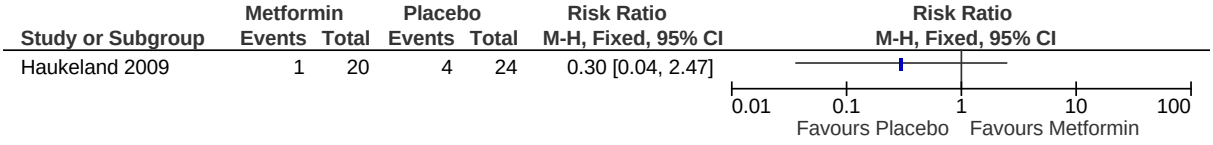
8.11.2.1 Progression of NAFLD (CRITICAL)

Figure 263: Proportion with improvement in NAFLD activity score [≥3 months to <12 months]



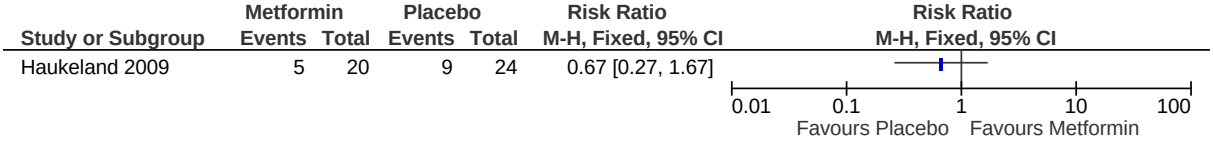
6

Figure 264: Proportion with improvement in fibrosis score [≥3 months to <12 months]



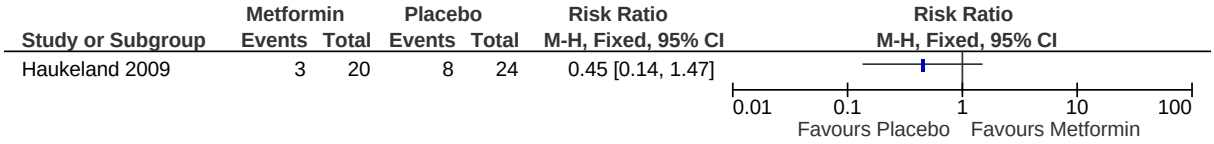
7

Figure 265: Proportion with improvement in steatosis [≥3 months to <12 months]



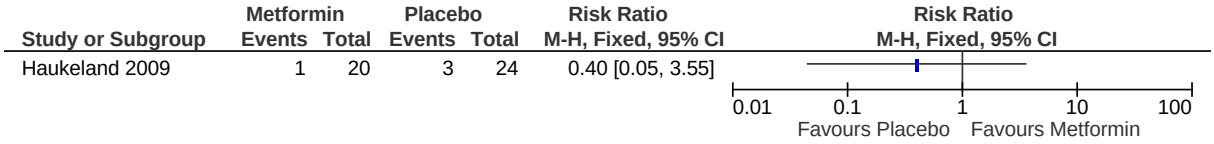
8

Figure 266: Proportion with improvement in lobular inflammation [≥3 months to <12 months]



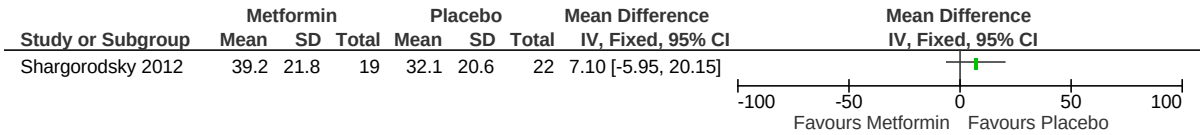
1

Figure 267: Proportion with improvement in ballooning [≥3 months to <12 months]



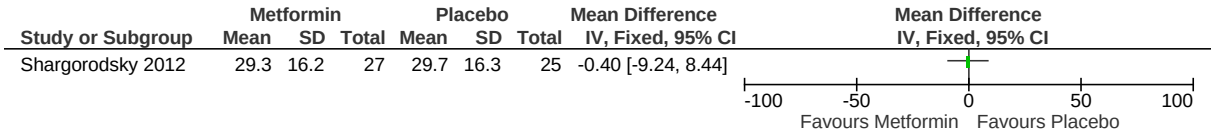
R.11.2.2 Liver function test (IMPORTANT)

Figure 268: Final ALT levels [>12 months]



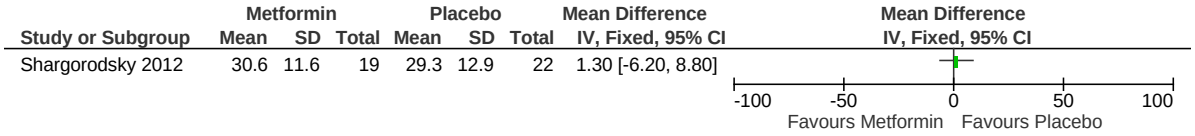
3

Figure 269: Final ALT levels [≥3 months to <12 months]



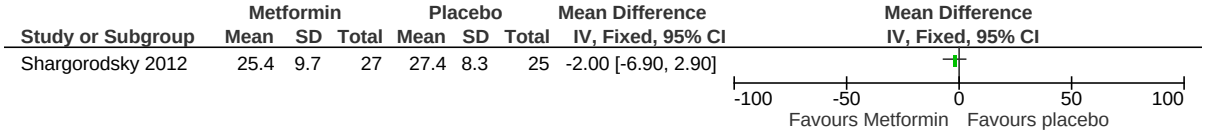
4

Figure 270: Final AST levels [>12 months]



5

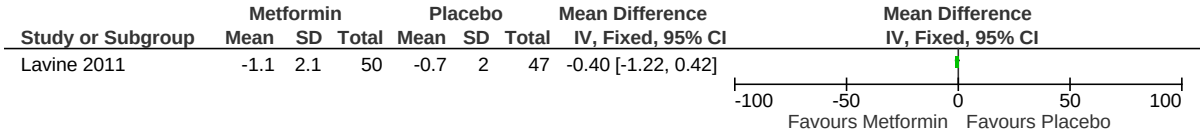
Figure 271: Final AST levels [≥3 months to <12 months]



1K.11.3 Metformin versus placebo for children and young people with NAFLD

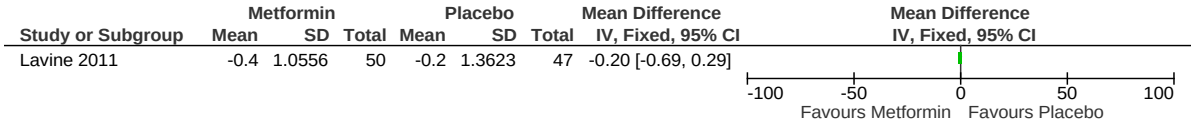
2K.11.3.1 Progression of NAFLD (CRITICAL)

Figure 272: Change in NAFLD activity score [>12 months]



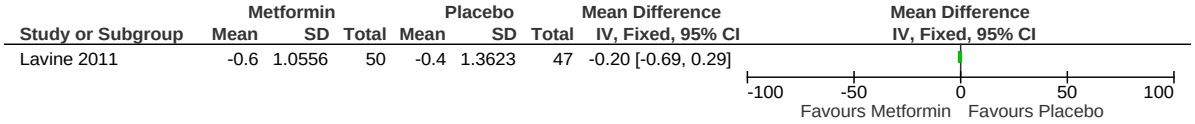
3

Figure 273: Change in fibrosis score [>12 months]



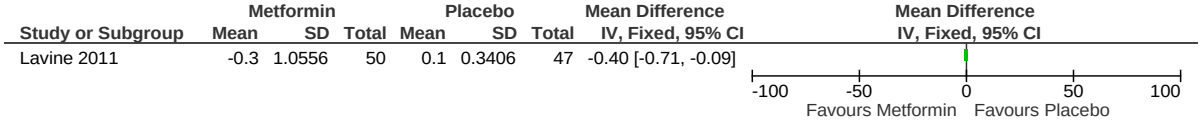
4

Figure 274: Change in steatosis score [>12 months]



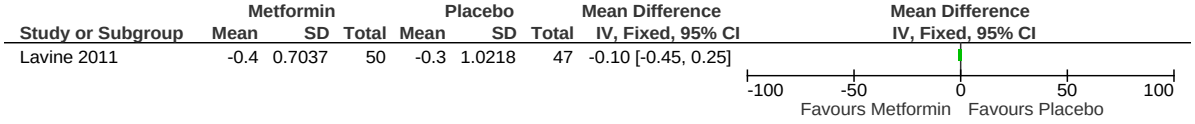
5

Figure 275: Change in ballooning degeneration score [>12 months]



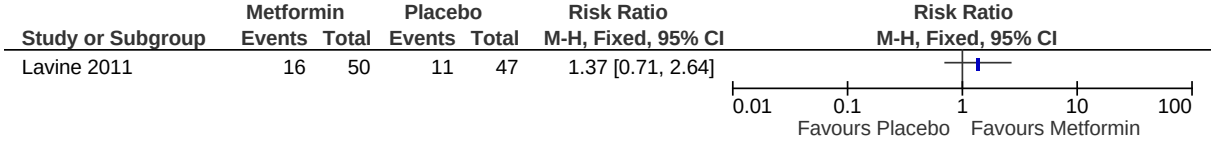
6

Figure 276: Change in lobular inflammation score [>12 months]



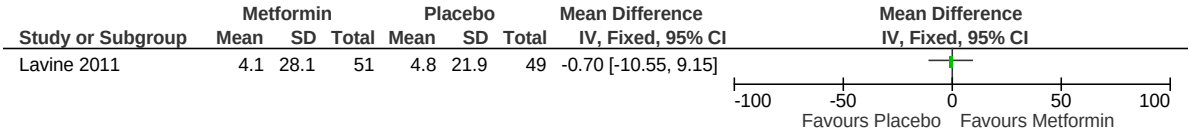
7

Figure 277: Resolution of NASH [>12 months]



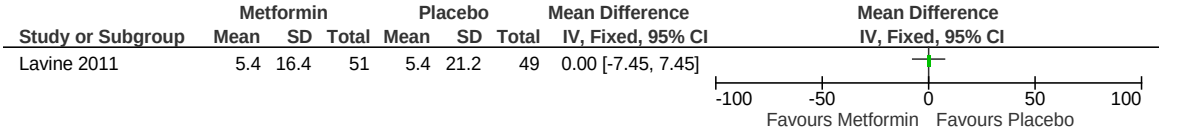
K.11.3.2 Quality of life (CRITICAL)

Figure 278: Change in parent-reported paediatric QOL-physical inventory [>12 months]



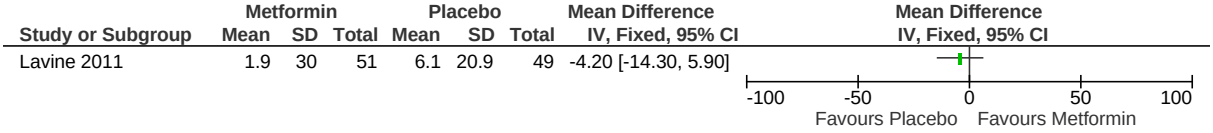
2

Figure 279: Change in children's self-reported paediatric QOL-physical inventory [>12 months]



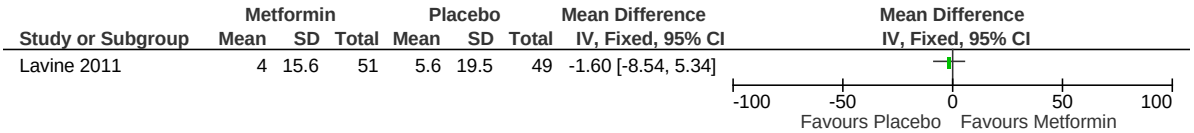
3

Figure 280: Change in parent-reported paediatric QOL-psychosocial inventory [>12 months]



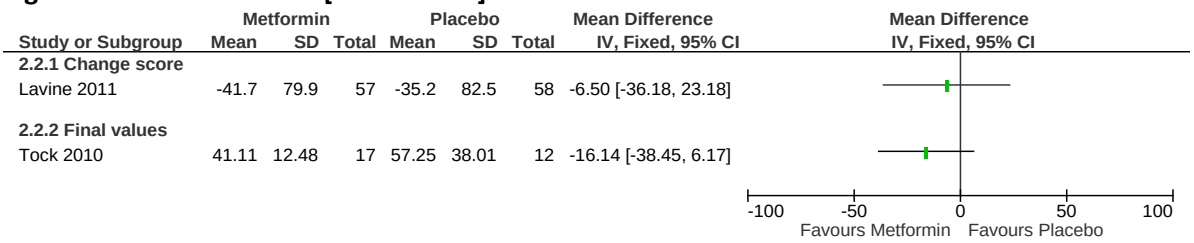
4

Figure 281: Change in children's self-reported paediatric QOL- psychosocial inventory [>12 months]



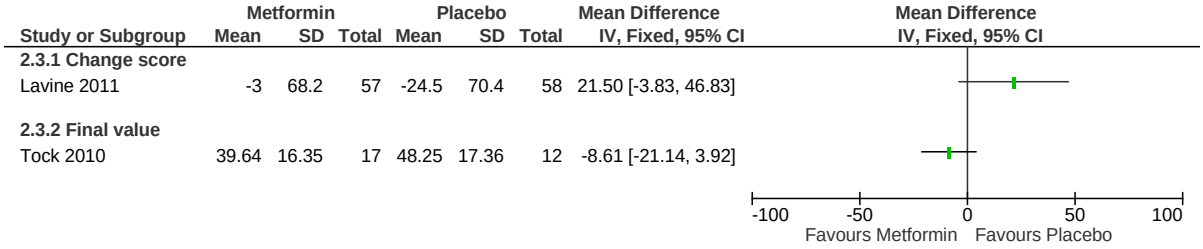
K.11.3.3 Liver function tests (IMPORTANT)

Figure 282: ALT levels [>12 months]



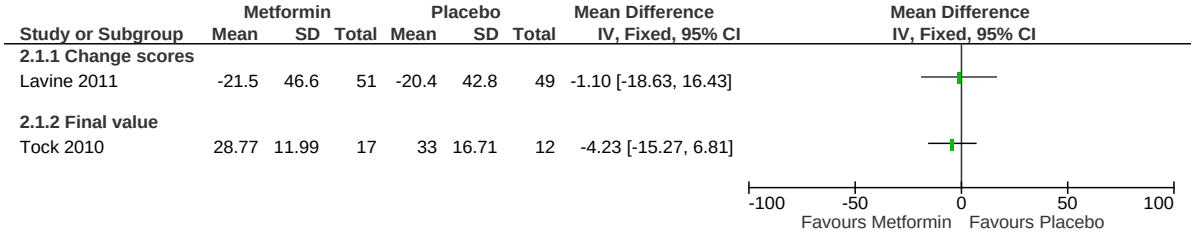
6

Figure 283: ALT levels [≥3 months to <12 months]



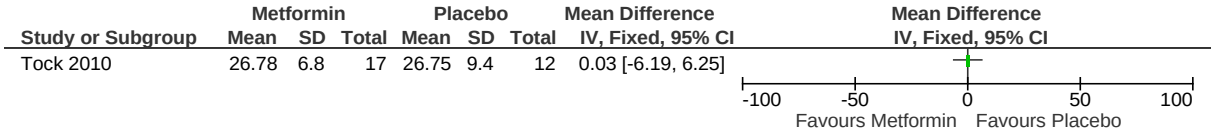
1

Figure 284: AST levels [>12 months]



2

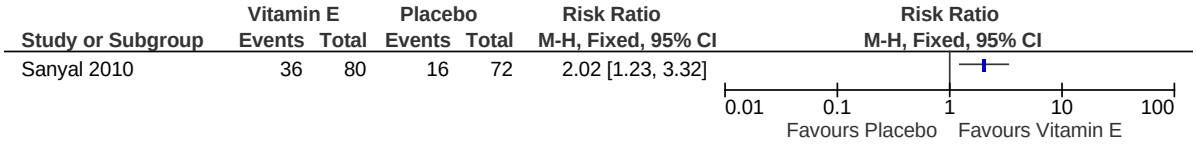
Figure 285: AST levels [≥3 months to <12 months]



3K.11.4 Vitamin E versus placebo for adults with NAFLD

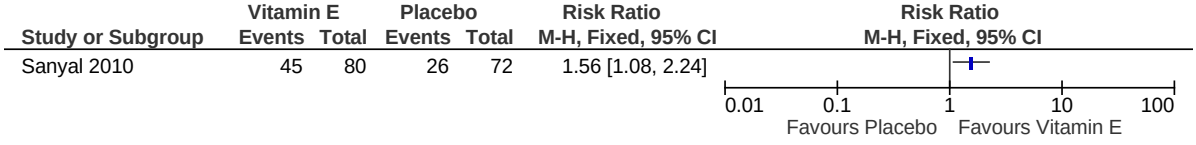
4.11.4.1 Progression of NAFLD (CRITICAL)

Figure 286: Improvement in histologic features of the liver [>12 months]



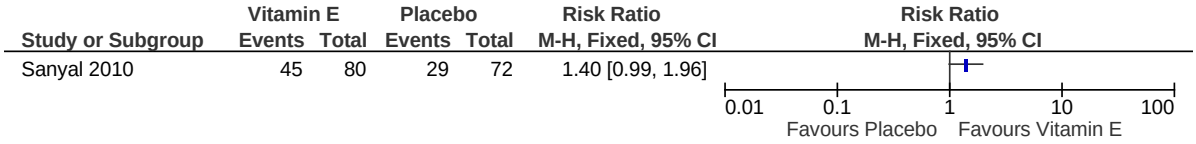
5

Figure 287: Improvement in steatosis [>12 months]



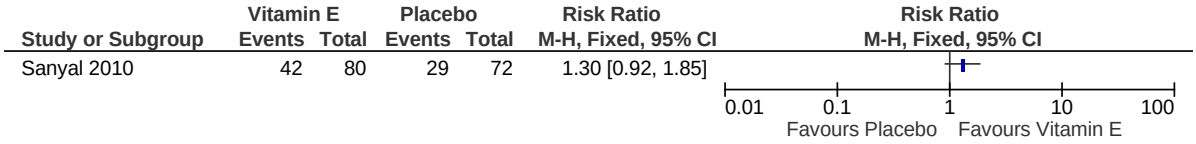
6

Figure 288: Improvement in lobular inflammation [>12 months]



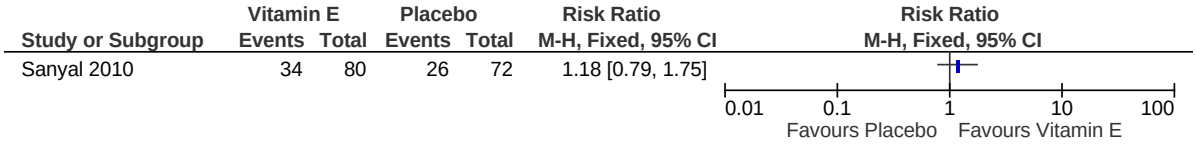
1

Figure 289: Improvement in hepatocellular ballooning [>12 months]



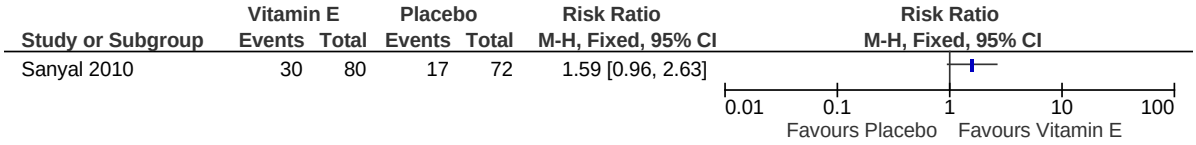
2

Figure 290: Improvement in fibrosis [>12 months}



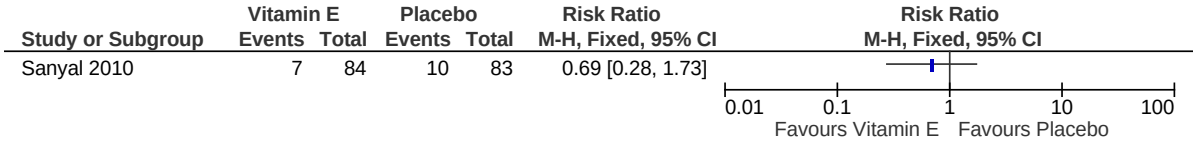
3

Figure 291: Resolution of definite NASH [>12 months]



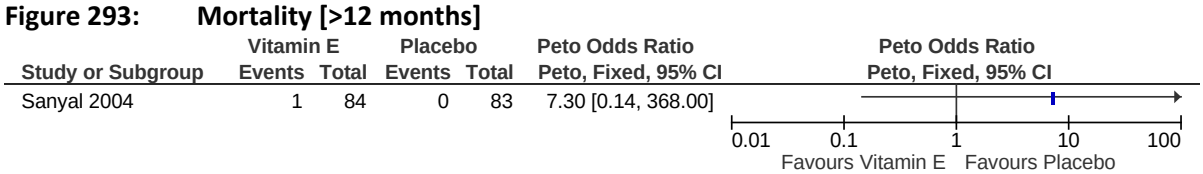
4.11.4.2 Serious adverse events (CRITICAL)

Figure 292: Serious adverse events [>12 months]



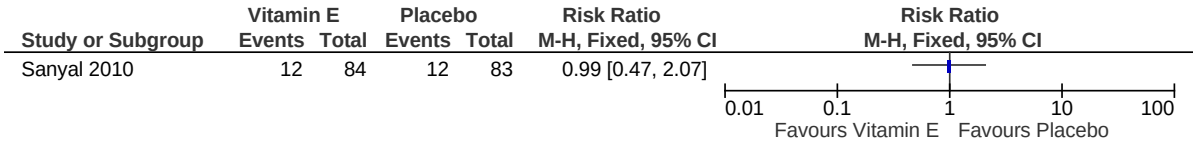
4.11.4.3 Mortality (CRITICAL)

Figure 293: Mortality [>12 months]



K.11.4.4 Adverse events (IMPORTANT)

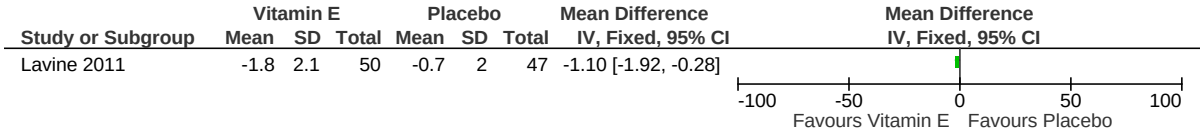
Figure 294: Adverse cardiovascular events [>12 months]



K.11.5 Vitamin E versus placebo for children and young people with NAFLD

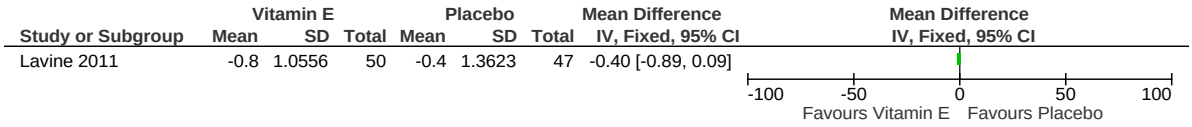
K.11.5.1 Progression of NAFLD (CRITICAL)

Figure 295: Change in NAFLD activity score [>12 months]



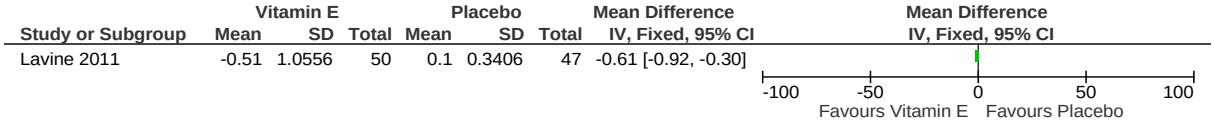
4

Figure 296: Change in fibrosis score [>12 months]



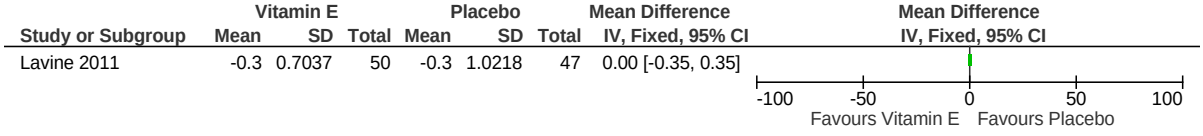
5

Figure 297: Change in ballooning degeneration score [>12 months]



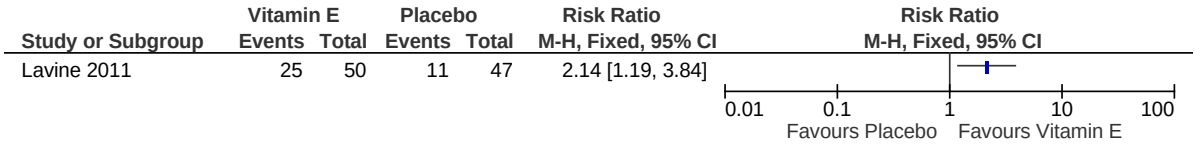
6

Figure 298: Change in lobular inflammation score [>12 months]



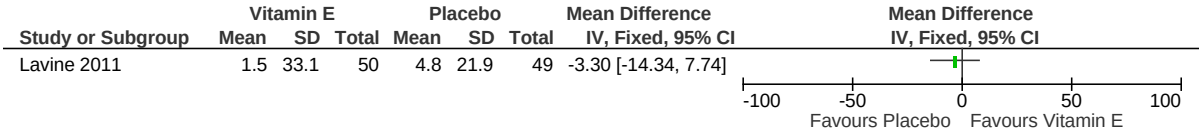
7

Figure 299: Resolution of NASH [>12 months]



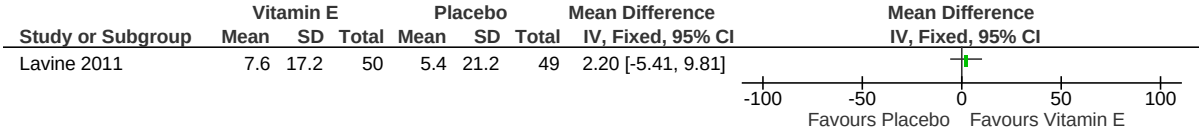
K.11.5.2 Quality of life (CRITICAL)

Figure 300: Change in parent-reported paediatric QOL-physical inventory [>12 months]



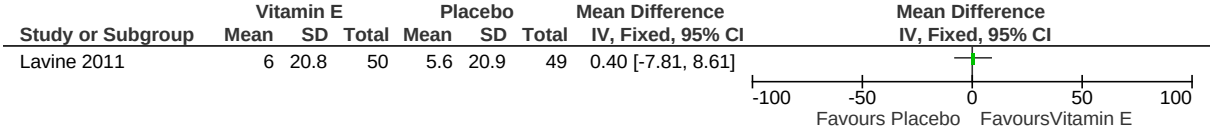
2

Figure 301: Change in children's self-reported paediatric QOL-physical inventory [>12 months]



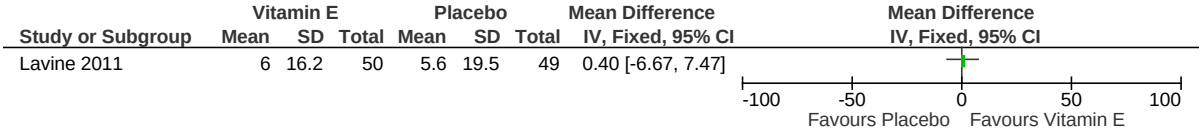
3

Figure 302: Change in parent-reported paediatric QOL-psychosocial inventory [>12 months]



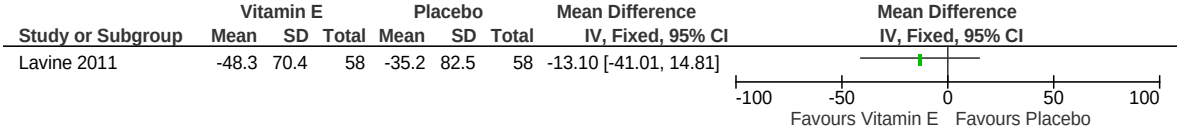
4

Figure 303: Change in children's self-reported paediatric QOL- psychosocial inventory [>12 months]



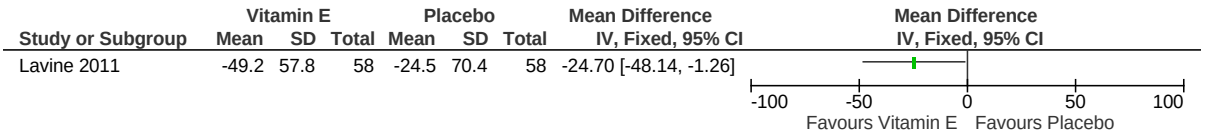
K.11.5.3 Liver function tests (IMPORTANT)

Figure 304: Change in ALT levels [>12 months]



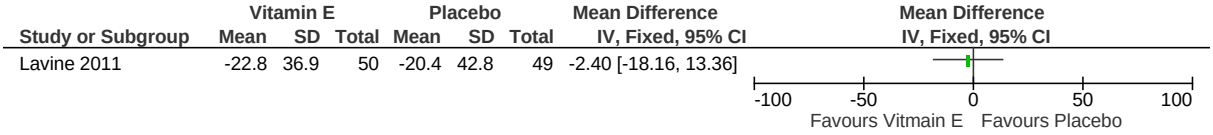
6

Figure 305: Change in ALT levels [≥3 months to <12 months]



7

Figure 306: Change in AST levels [>12 months]

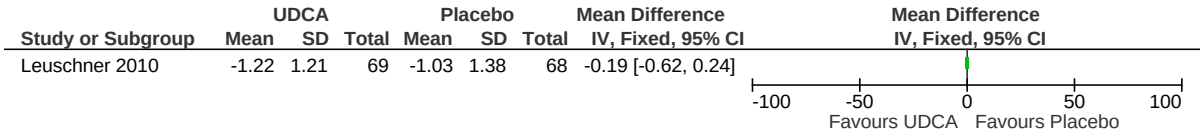


1

2K.11.6 Ursodeoxycholic acid (UCDA) versus placebo for adults with NAFLD

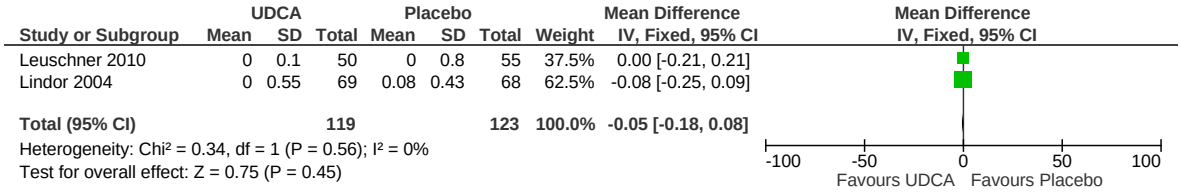
3K.11.6.1 Progression of NAFLD (CRITICAL)

Figure 307: Change in NAFLD activity score [>12 months]



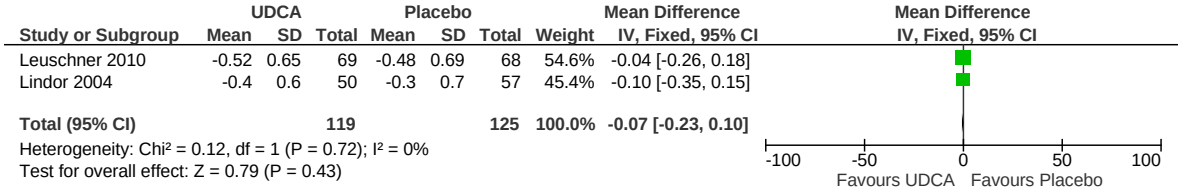
4

Figure 308: Change in fibrosis [>12 months]



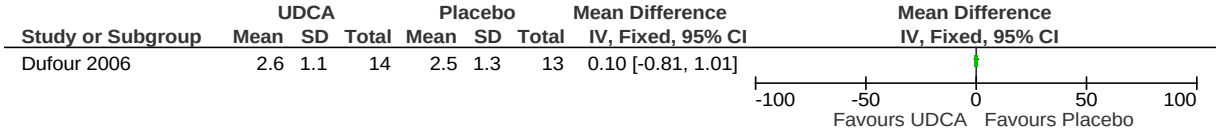
5

Figure 309: Change in steatosis [>12 months]



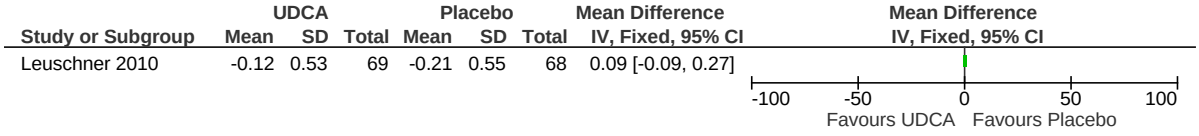
6

Figure 310: Final steatosis values [>12 months]



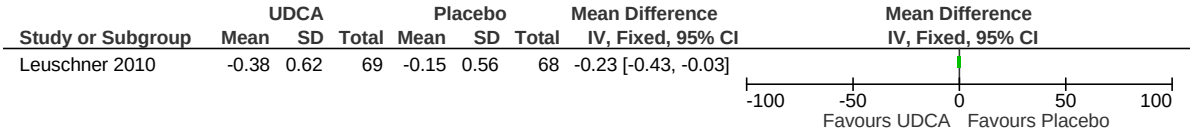
7

Figure 311: Change in ballooning [>12 months]



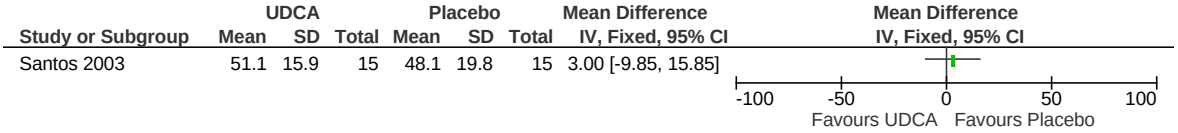
1

Figure 312: Change in lobular inflammation [>12 months]



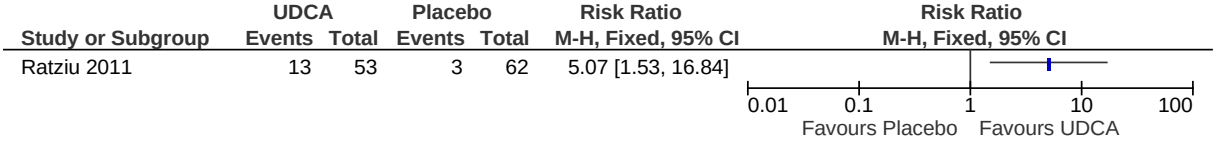
2

Figure 313: Change in hepatic density [>12 months]



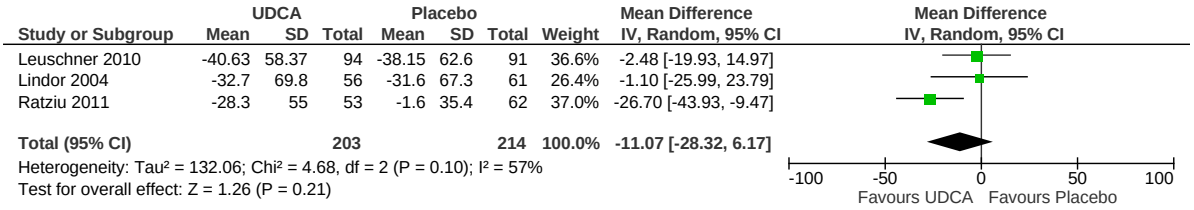
8.11.6.2 Liver function tests (IMPORTANT)

Figure 314: Normalised ALT levels [>12 months]



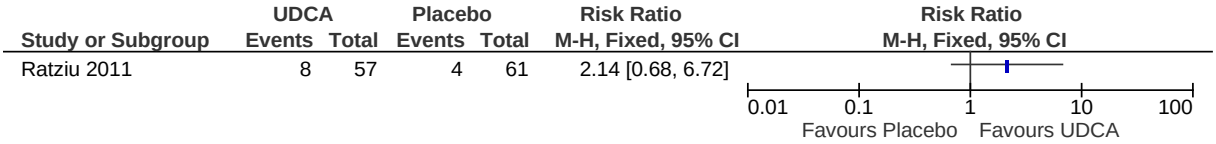
4

Figure 315: Change in ALT levels [>12 months]



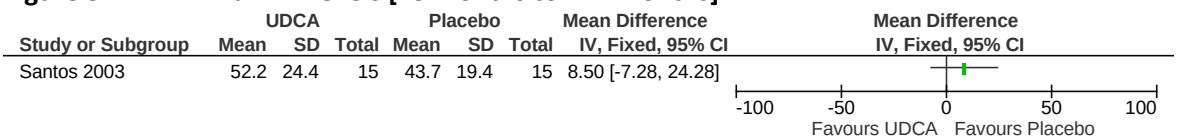
5

Figure 316: Normalised ALT levels [≥3 months to <12 months]



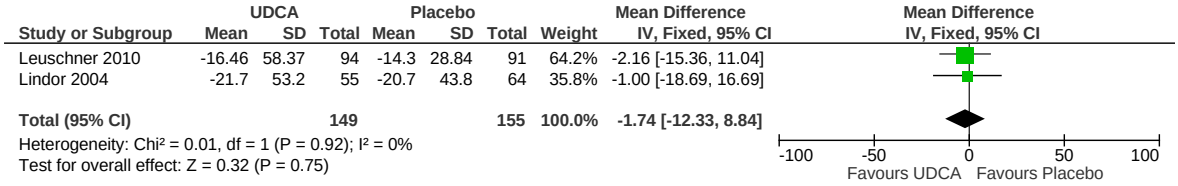
6

Figure 317: Final ALT levels [≥3 months to <12 months]



7

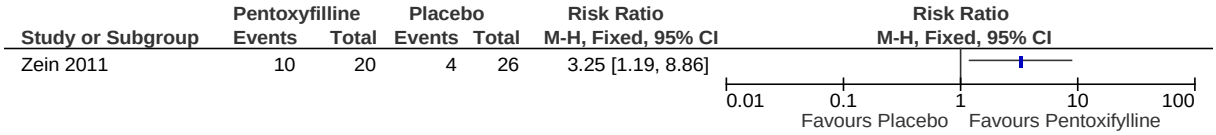
Figure 318: Change in AST levels [>12 months]



1K.11.7 Pentoxifylline versus placebo for adults with NAFLD

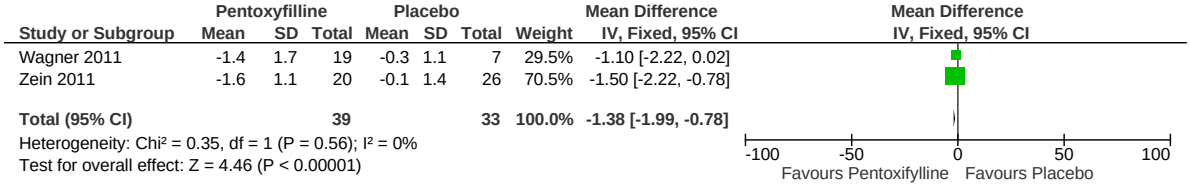
2.11.7.1 Progression of NAFLD (CRITICAL)

Figure 319: NAFLD activity score decreased by ≥2 points [>12 months]



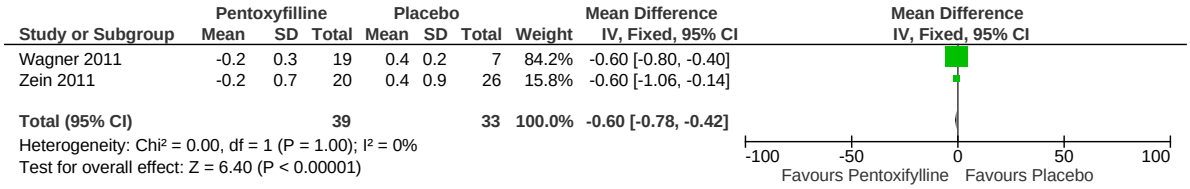
3

Figure 320: Change in NAFLD activity score [>12 months]



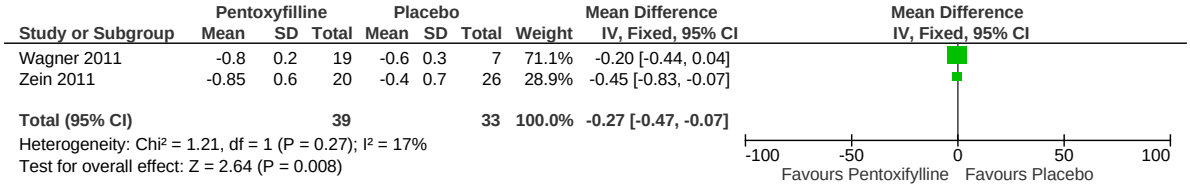
4

Figure 321: Change in fibrosis [>12 months]



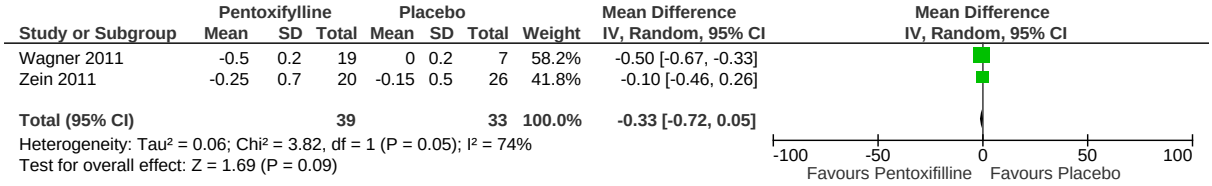
5

Figure 322: Change in steatosis [>12 months]



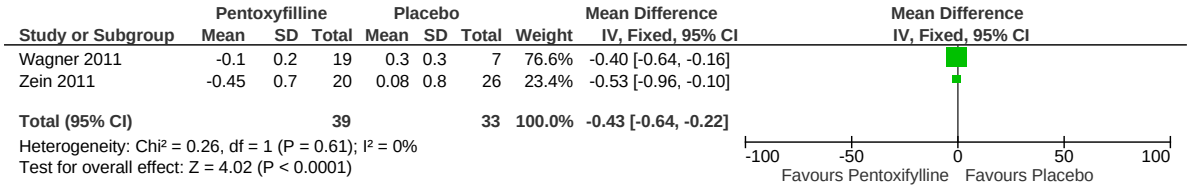
6

Figure 323: Change in ballooning [>12 months]



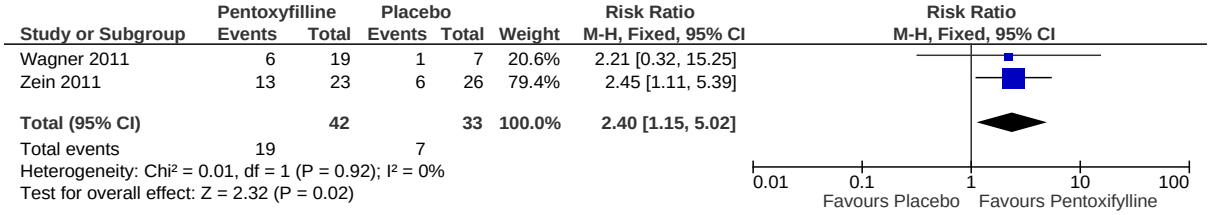
1

Figure 324: Change in lobular inflammation [>12 months]



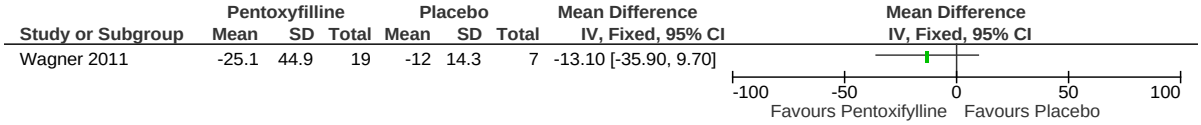
R.11.7.2 Liver function tests (IMPORTANT)

Figure 325: Normalisation in ALT levels [>12 months]



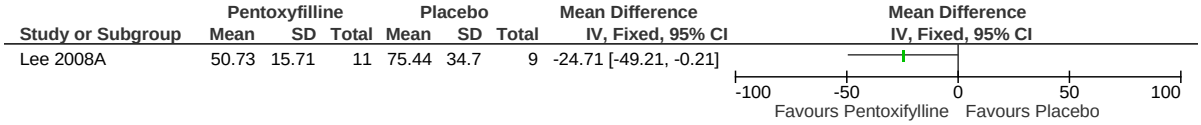
3

Figure 326: Change in ALT levels [>12 months]



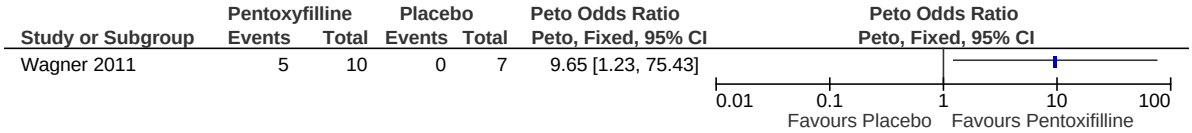
4

Figure 327: Final ALT levels [≥3 months to <12 months]



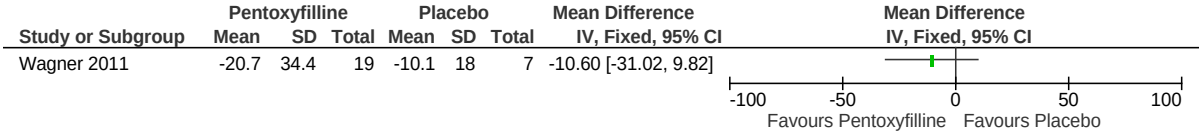
5

Figure 328: Normalisation of AST levels [>12 months]



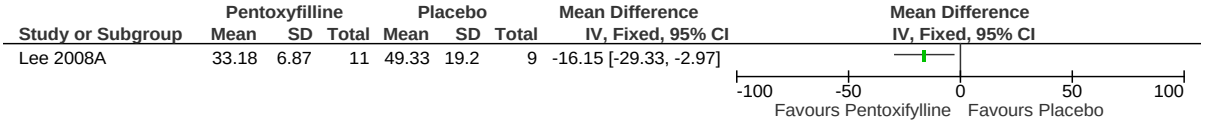
6

Figure 329: Change in AST levels [>12 months]



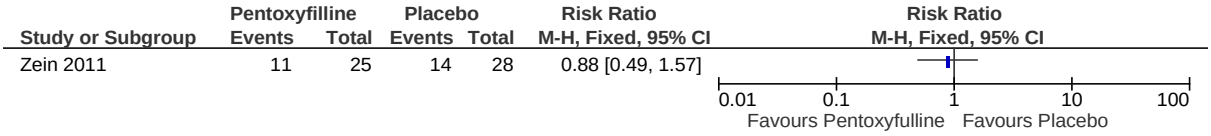
1

Figure 330: Final AST levels [≥3 months to <12 months]



K.11.7.3 Adverse events (IMPORTANT)

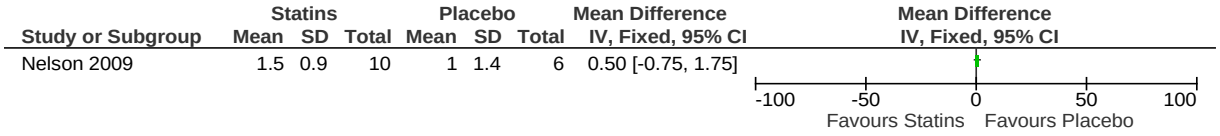
Figure 331: Adverse events [>12 months]



K.11.8 Statins versus placebo for adults with NAFLD

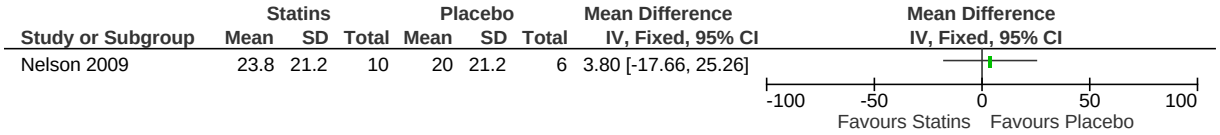
K.11.8.1 Progression of NAFLD (CRITICAL)

Figure 332: Final fibrosis stage [>12 months]



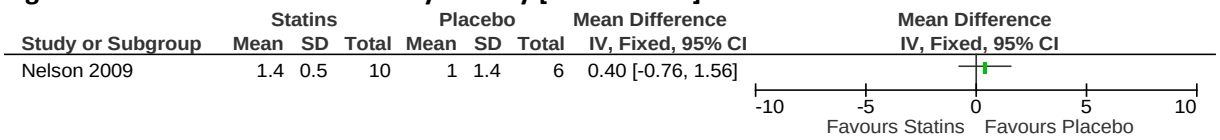
5

Figure 333: Final percentage of steatosis [>12 months]



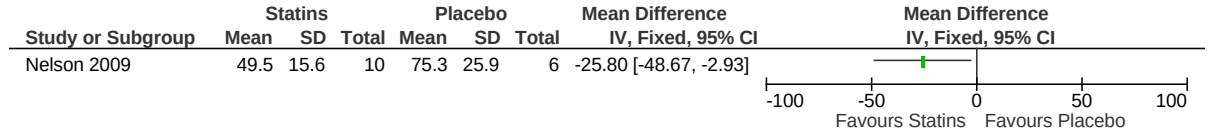
6

Figure 334: Necroinflammatory activity [>12 months]



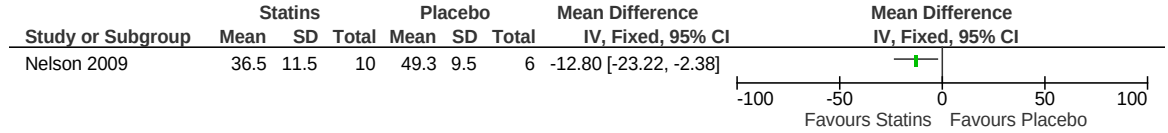
K.11.8.2 Progression of NAFLD (CRITICAL)

Figure 335: Final ALT levels [>12 months]



2

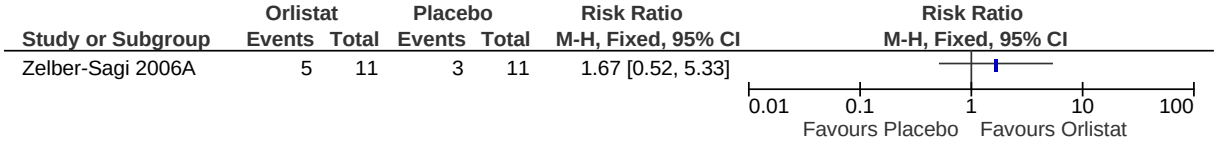
Figure 336: Final AST levels [>12 months]



K.11.9 Orlistat versus placebo for adults with NAFLD

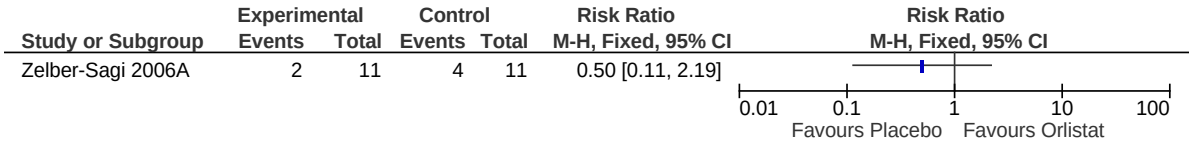
K.11.9.1 Progression of NAFLD (CRITICAL)

Figure 337: ≥1 degree of improvement in fibrosis [≥3 months to <12 months]



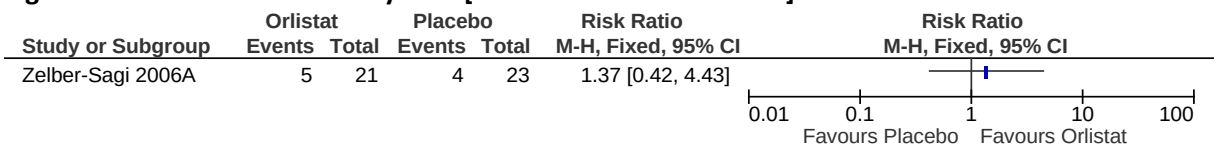
5

Figure 338: Improved steatosis [≥3 months to <12 months]



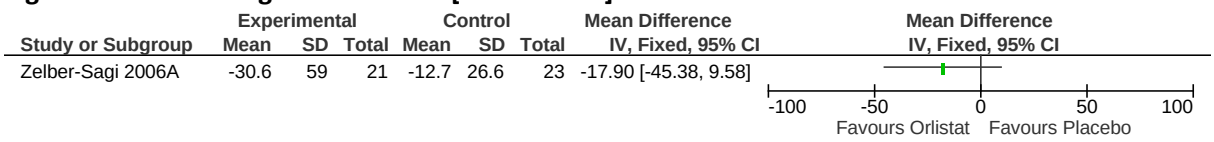
6

Figure 339: Reversal of fatty liver [≥3 months to <12 months]



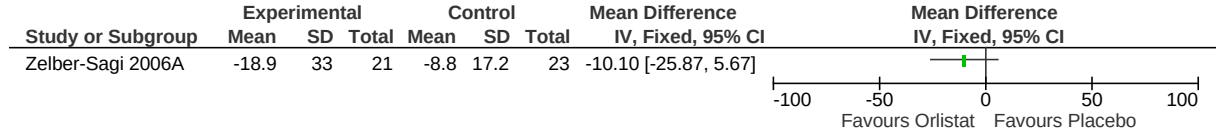
K.11.9.2 Liver function tests (IMPORTANT)

Figure 340: Change in ALT levels [>12 months]



8

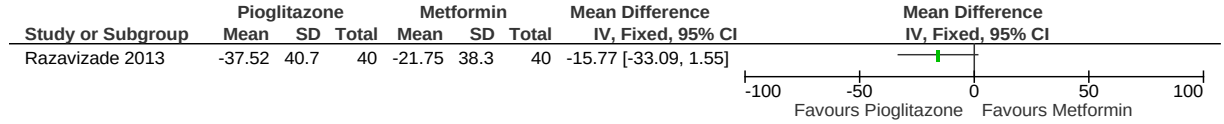
Figure 341: Change in AST levels [>12 months]



K11.10 Pioglitazone versus Metformin for adults with NAFLD

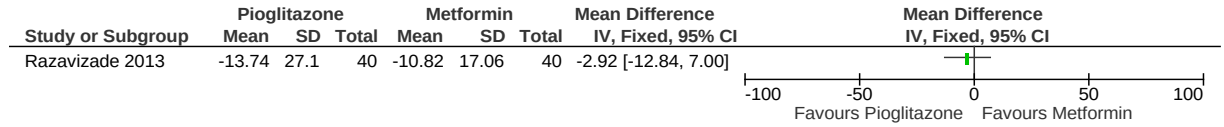
K11.10.1 Liver function tests (IMPORTANT)

Figure 342: Change in ALT levels [>12 months]



3

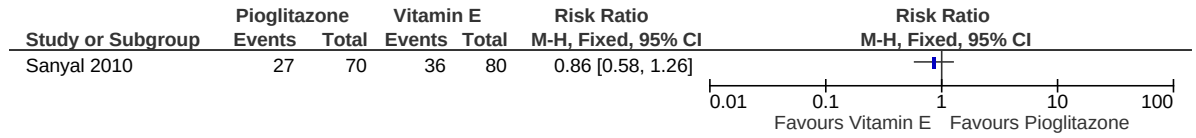
Figure 343: Change in AST levels [>12 months]



K11.11 Pioglitazone versus Vitamin E for adults with NAFLD

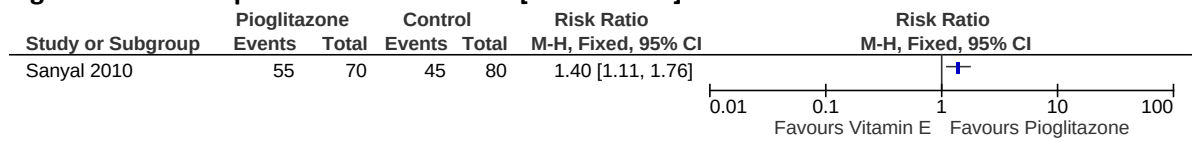
K11.11.1 Progression of NAFLD (CRITICAL)

Figure 344: Improvement in histologic features of the liver [>12 months]



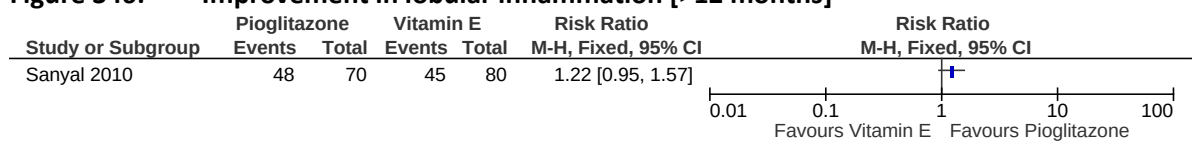
6

Figure 345: Improvement in steatosis [>12 months]



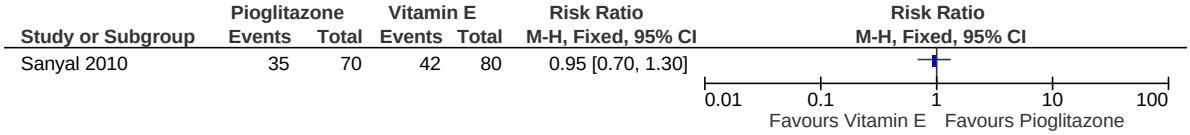
7

Figure 346: Improvement in lobular inflammation [>12 months]



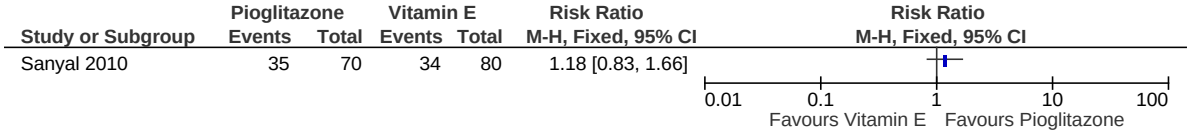
8

Figure 347: Improvement in hepatocellular inflammation [>12 months]



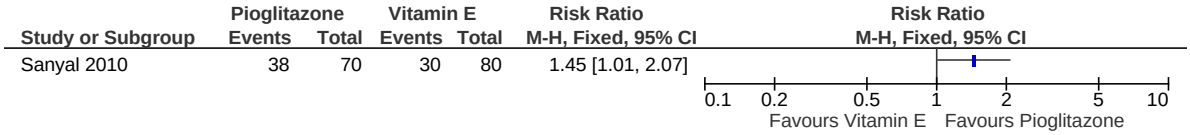
1

Figure 348: Improvement in fibrosis [>12 months]



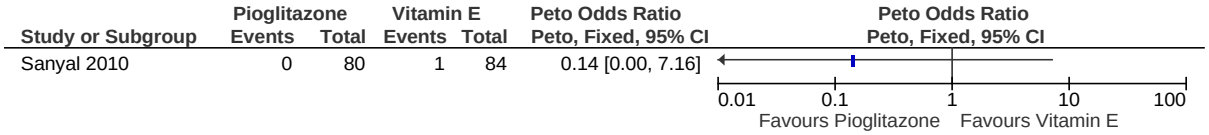
2

Figure 349: Resolution of definite NASH [>12 months]



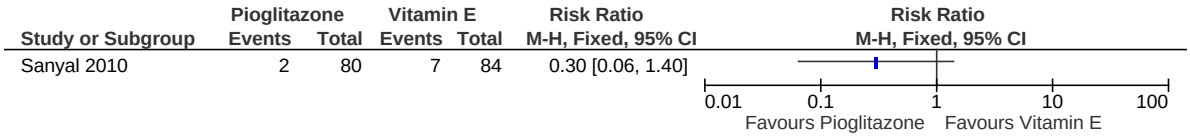
K31 11.11.2 Mortality (CRITICAL)

Figure 350: Mortality [>12 months]



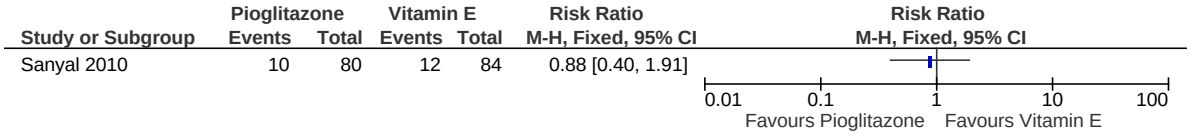
K41 11.11.3 Serious adverse events (CRITICAL)

Figure 351: Serious adverse events [>12 months]



K51 11.11.4 Adverse events (IMPORTANT)

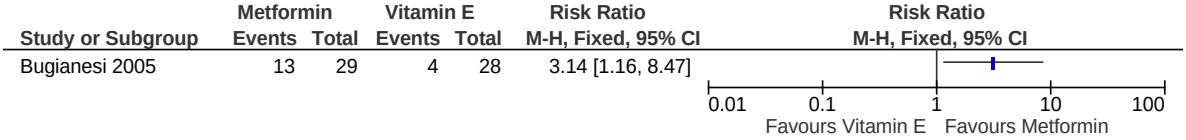
Figure 352: Adverse cardiovascular events [>12 months]



K.11.12 Metformin versus Vitamin E for adults with NAFLD

K.11.12.1 Liver function tests (IMPORTANT)

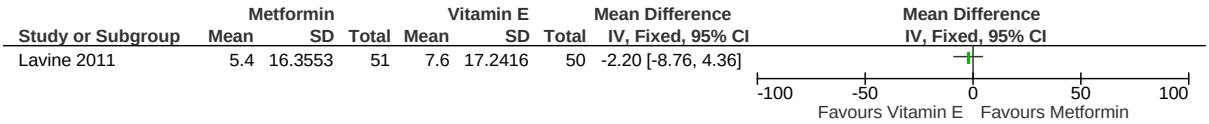
Figure 353: Normalised ALT levels [>12 months]



K.11.13 Metformin versus Vitamin E for children and young people with NAFLD

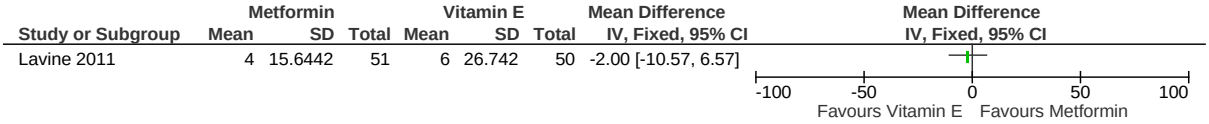
K.11.13.1 Health related quality of life (CRITICAL)

Figure 354: Change in self-reported paediatric QoL Inventory (physical, 0-100) [>12 months]



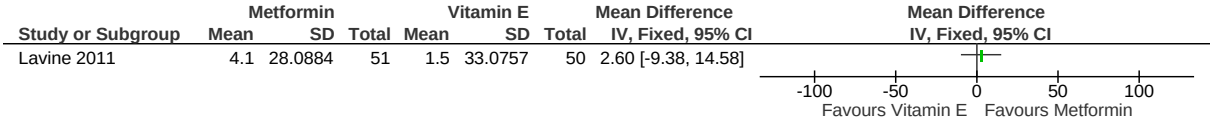
5

Figure 355: Change in self-reported paediatric QoL Inventory (psychological 0-100) [>12 months]



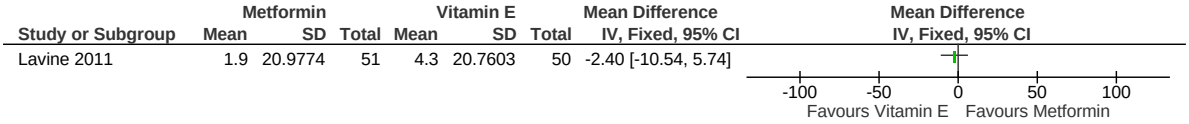
6

Figure 356: Change in parent/guardian-reported paediatric QoL Inventory (physical, 0-100) [>12 months]



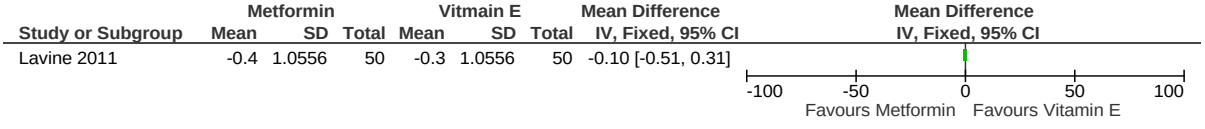
7

Figure 357: Change in Parent/guardian-reported paediatric QoL Inventory (physical, 0-100) [>12 months]



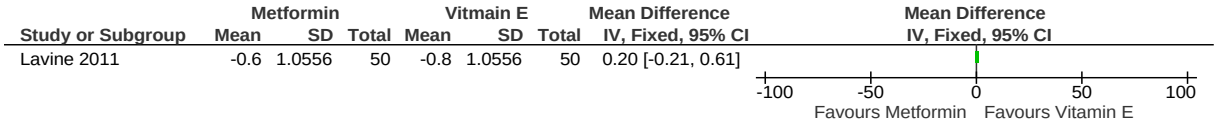
K.11.13.2 Progression of NAFLD (CRITICAL)

Figure 358: Change in fibrosis score [>12 months]



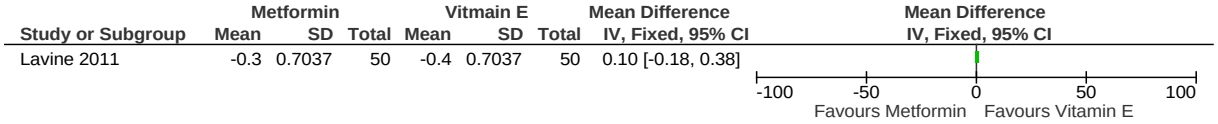
1

Figure 359: Change in steatosis score [>12 months]



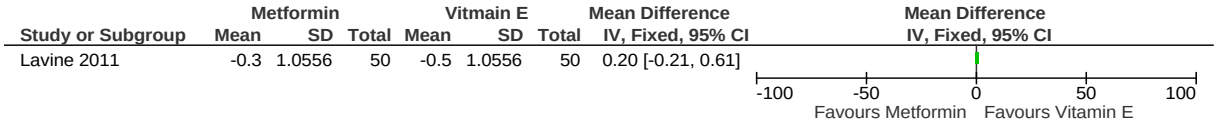
2

Figure 360: Change in lobular inflammation score [>12 months]



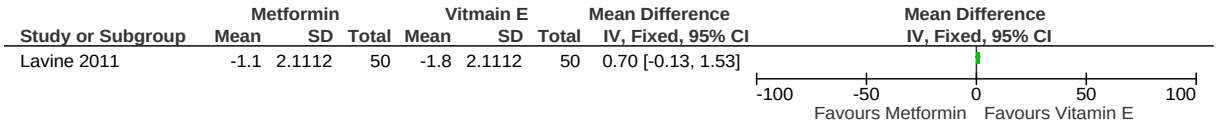
3

Figure 361: Change in ballooning degeneration score [>12 months]



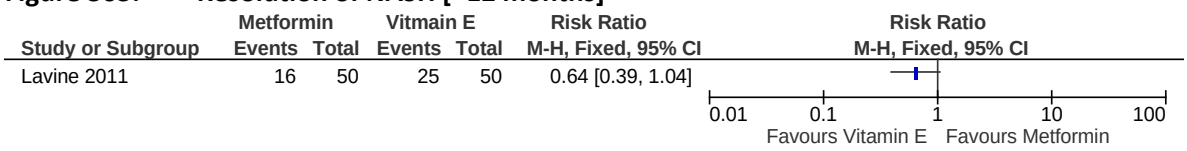
4

Figure 362: Change in NAFLD activity score [>12 months



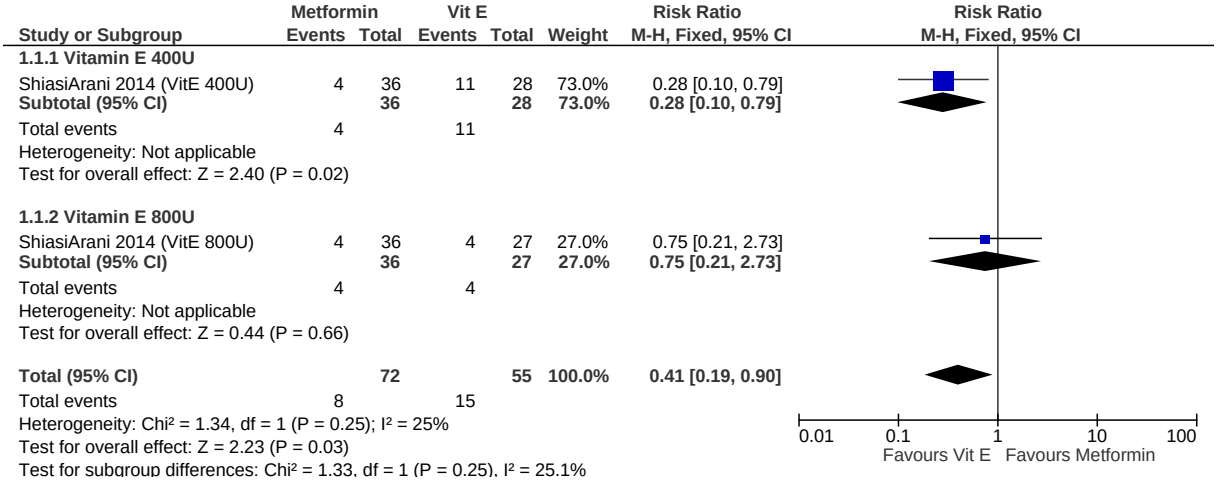
5

Figure 363: Resolution of NASH [>12 months]



6

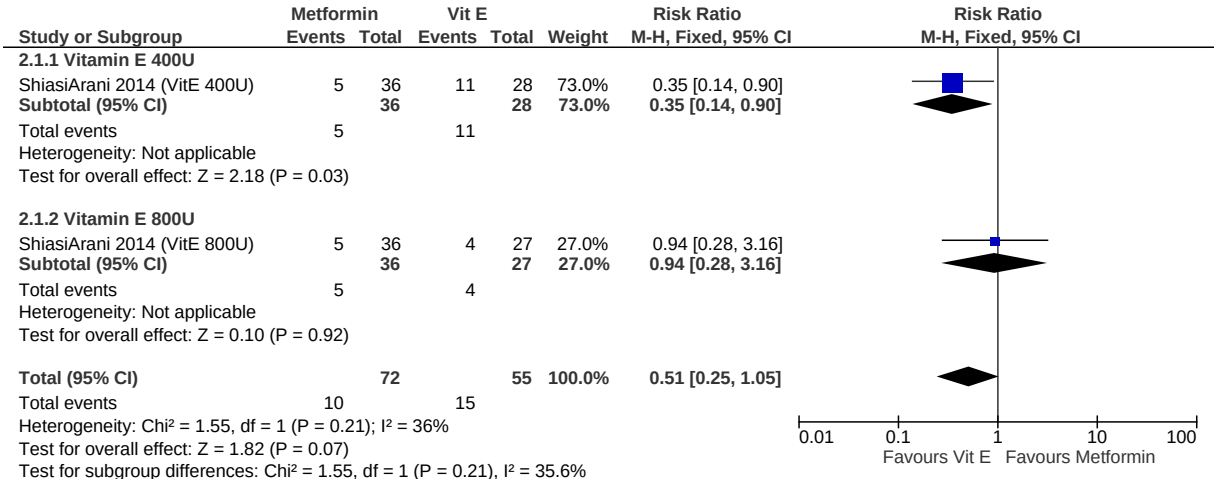
Figure 364: Remission of NAFLD (ultrasound), Metformin 1g/day [<12 months]



NOTE: double counting of metformin group

1

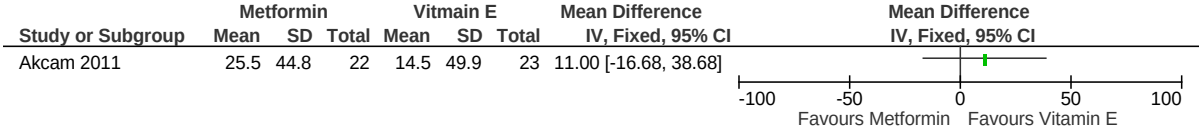
Figure 365: Remission of NAFLD (ultrasound), Metformin 1.5g/day [<12 months]



NOTE: double counting of metformin group

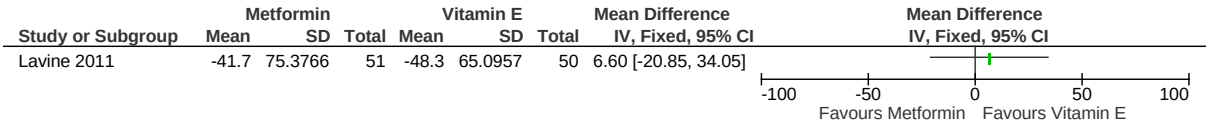
K211.13.3 Liver function tests (IMPORTANT)

Figure 366: Change in triglycerides [≥3 months to <12 months]



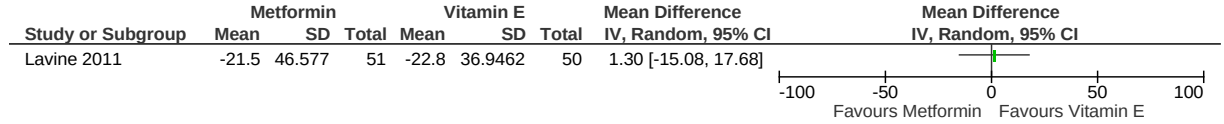
3

Figure 367: Change in ALT levels [>12 months]



4

Figure 368: Change in AST levels [>12 months]



K11.13.4 Adverse events (IMPORTANT)

Figure 369: Adverse events [≥3 months to <12 months]

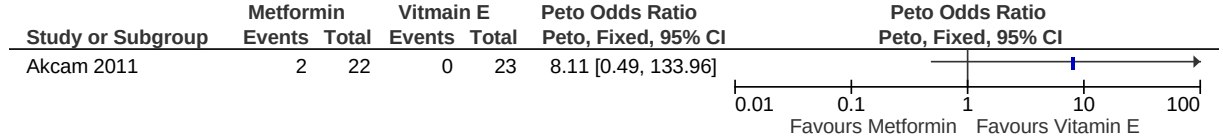


Figure 370:

K11.14 Pentoxifylline versus Pioglitazone for adults with NAFLD

K11.14.1 Progression of NAFLD (CRITICAL)

Figure 371: Final fibrosis stage [≥3 months to <12 months]

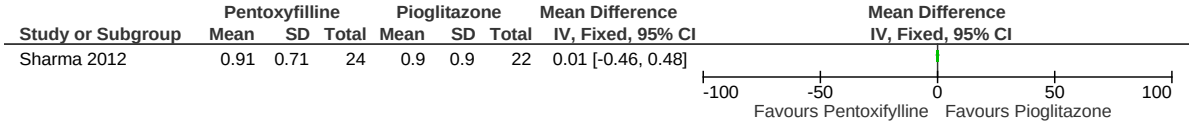


Figure 372: Final steatosis grade [≥3 months to <12 months]

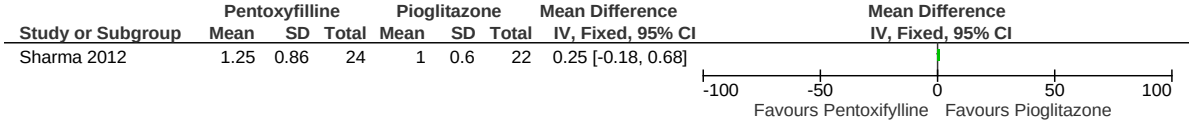


Figure 373: Final hepatocellular ballooning [≥3 months to <12 months]

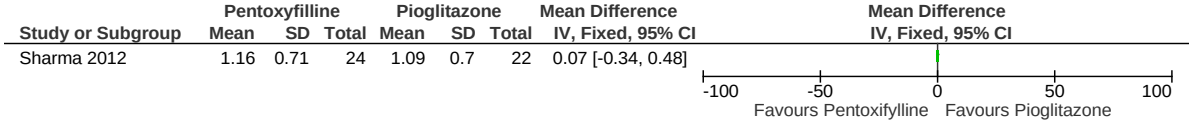
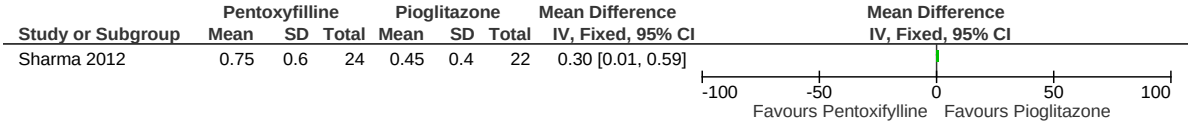
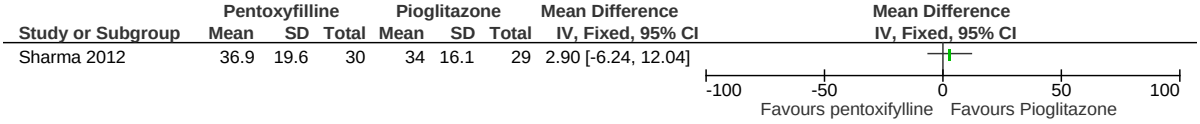


Figure 374: Final lobular inflammation [≥3 months to <12 months]



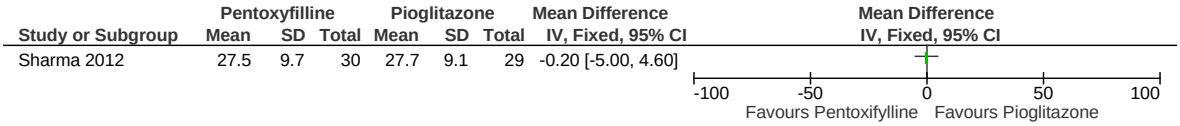
K11.14.2 Liver function tests (IMPORTANT)

Figure 375: Final ALT levels [≥3 months to <12 months]



2

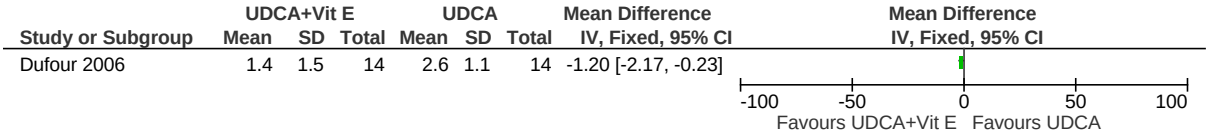
Figure 376: Final AST levels [≥3 months to <12 months]



K11.15 UDCA + Vitamin E versus UDCA alone for adults with NAFLD

K11.15.1 Progression of NAFLD (CRITICAL)

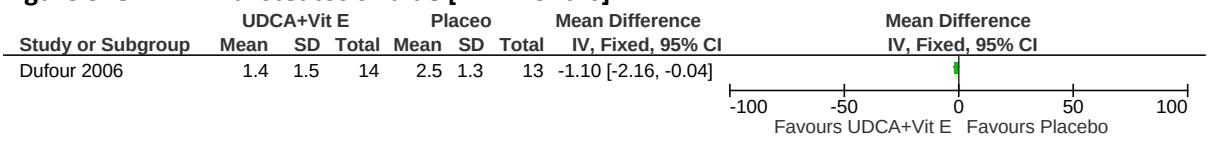
Figure 377: Final steatosis value [>12 months]



K11.16 UDCA + Vitamin E versus Placebo alone for adults with NAFLD

K11.16.1 Progression of NAFLD (CRITICAL)

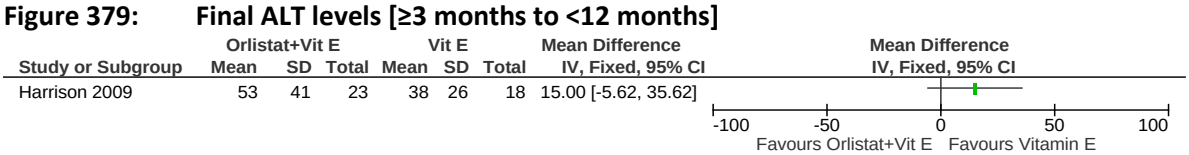
Figure 378: Final steatosis value [>12 months]



K11.17 Orlistat + Vitamin E versus Vitamin E alone for adults with NAFLD

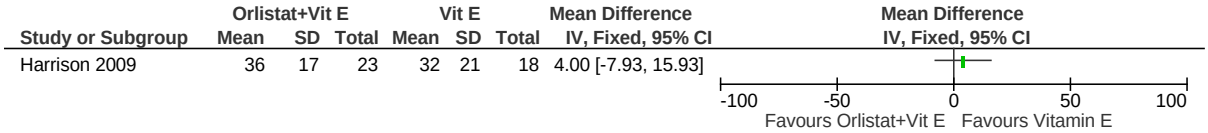
K11.17.1 Liver function tests (IMPORTANT)

Figure 379: Final ALT levels [≥3 months to <12 months]



1

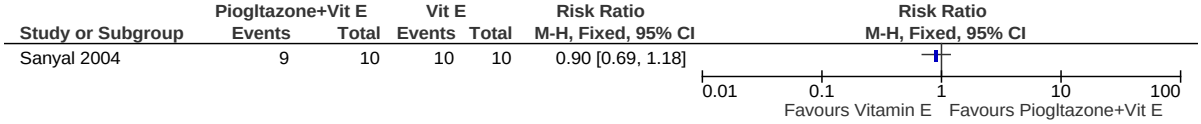
Figure 380: Final AST levels [≥3 months to <12 months]



K2 11.18 Pioglitazone + Vitamin E versus Vitamin E alone for adults with NAFLD

K3 11.18.1 Liver function tests (IMPORTANT)

Figure 381: Normalisation of ALT levels [≥3 months to <12 months]



Appendix L: Diagnostic meta-analysis

Results

The results of each diagnostic meta-analysis are presented in Chapter 6 (diagnosis of NAFLD) and Chapter 7 (diagnosing the severity of NAFLD) in the full guideline.

Analysis

The bivariate method utilises a logistic regression on the true positives, true negatives, false positives and false negatives reported in the studies and is parameterised as follows[811,992,993]:

$$TP_i \sim Binomial(\pi_{Ai}, (TP_i + FN_{i)})$$

$$TN_i \sim Binomial(\pi_{Bi}, (FP_i + TN_i))$$

$$\theta_{Ai} = ln\left(\frac{\pi_{Ai}}{1-\pi_{Ai}}\right)$$

$$\theta_{Bi} = ln\left(\frac{\pi_{Bi}}{1-\pi_{Bi}}\right)$$

$$\begin{pmatrix}\theta_{Ai}\\ \theta_{Bi}\end{pmatrix} \sim N\left(\begin{pmatrix}\theta_A\\ \theta_B\end{pmatrix}, \Sigma\right)$$

$$\Sigma = \begin{pmatrix}\sigma_A^2 & \sigma_{AB}\\ \sigma_{AB} & \sigma_B^2\end{pmatrix}$$

$$\alpha = \frac{e^{\theta_A}}{1+e^{\theta_A}}$$

$$\beta = \frac{e^{\theta_B}}{1+e^{\theta_B}}$$

Where:

TP_i, TN_i, FP_i and FN_i represent the true positives, true negatives, false positives and false negatives, respectively, reported in study i.

$\theta_{Ai}$and θ_{Bi}represent the sensitivity and specificity calculated from the results of study i on the log odds scale.

θ_A and θ_B represent the mean pooled sensitivity and specificity on the log odds scale, i.e. the results of the meta analysis.

Σ represents the variance-covariance matrix of the pooled sensitivity and specificity on the log odds scale.

α and β represent the pooled sensitivity and specificity on the natural scale; these are the final summary estimates of interest.

The model above was fitted in WinBUGS. Using the output from WinBUGS, we constructed and plotted confidence regions and, where appropriate ROC curves, using methods outlined by Novelli[708] in Microsoft Excel.

As it was a Bayesian analysis, the evidence distribution is weighted by a distribution of prior beliefs. Vague non-informative priors were used for all parameters. For each analysis, a series of 50,000 burn-in simulations were run to allow convergence and then a further 50,000 simulations were run to produce the outputs. Convergence was assessed by investigating density plots, auto correlation plots and history plots for parameters of interest.

In cases where cell counts were 0, 1 was added to each category (true positives, false positives, true negatives, false negatives) to ensure the model was able to run, whilst not significantly distorting the results.

WinBUGS code[709]

Model

```
{

for (i in 1:NS)

        {

        TotP[i]<-TP[i] + FN[i]
        TotN[i]<-FP[i] + TN[i]
        TP[i] ~ dbin(p[i , 1] , TotP[i])
        TN[i] ~ dbin(p[i , 2]  , TotN[i])

                for (j in 1:2)

                {
                logit(p[i , j]) <- MeanS[i , j]
                }
        MeanS[i , 1:2] ~ dmnorm(md[] , sigma[,])

        }
        sigma[1:2,1:2]~dwish(R[,] , 2)
        Sigma.sq[1:2,1:2] <- inverse(sigma[,])

                for (i in 1:2)
                        {
                        parms[i] <- exp(md[i])/(1+exp(md[i]))
                        }

        sens <- parms[1]
        spec<- parms[2]


                for (i in 1:2)
                        {
                        md[i] ~ dnorm(0 , 0.001)
                        }

                sensitivity.bar <- exp(md[1])/(1+ exp(md[1]))
        specificity.bar <- exp(md[2])/(1+exp(md[2]))
```

```
    }



}
```

Data

```
list(NS= Number of studies goes here)

list(R = structure(
        .Data = c(1, 0,
                0, 1), .
        Dim = c(2, 2))
```

Cell Counts for each strategy are entered below, in place of the ni values

```
TP=True positives
FP=False positives
FN=False negatives
TN=True negatives

TP[]    FP[]    FN[]    TN[]
n1      n2      n3      n4
END
```

Initial conditions

```
list(md=c(0,0))
```

1 Appendix M: Excluded clinical studies

2 M.1 Risk factors for NAFLD

3 **Table 45: Studies excluded from the clinical review for risk factors for NAFLD**

Reference	Reason for exclusion
ABBAS 2013[3]	Incorrect population (mixed adults and children)
ABRAMS 2004[10]	Incorrect population
AKAHANE 2013[22]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
AKAHOSHI 2001[23]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
AKHA 2010[25]	No multivariate analysis
ALAVIAN 2009[34]	Wrong study design: cross-sectional (predictors of NAFLD)
ALAZMI 2006[35]	Wrong outcomes for multivariate analysis: predictors of cirrhosis.
ALDERETE 2013[37]	Unclear study results
ALHAMOUDI 2012[31]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
ALKASSABANYY 2014[40]	Wrong study design: cross-sectional (predictors of NAFLD)
ALLER 2008[48]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
ALMOBARAK 2014[49]	No multivariate analysis
AMARAPURKA 2002[55]	No multivariate analysis.
AMARAPURAKA 2004[57]	
AMARAPURKA 2006[54]	Adults study. Predictors of NASH/fibrosis: cross-sectional study adjusted multivariate analysis for <3 of our pre-specified confounders.
AMARAPURKA 2008[56]	No multivariate analysis.
ANGELICO 2003[64]	No multivariate outcomes reported
ANGULO 1999[68]	Adult study: predictors of NASH/fibrosis: cross-sectional study adjusted multivariate analysis for <3 of our pre-specified confounders.
ARDIGO 2005[72]	Not looking at risk factors for NAFLD or NASH/fibrosis
ARGO 2009[77]	Systematic review: incorrect methodology
ARSLAN 2005[81]	No multivariate analysis.
ATABEK2014[86]	Wrong study design: cross-sectional
AYONRINDE2015[95]	Wrong study design: cross-sectional
BABUSIK 2012[97]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
BAE 2010[100]	Irrelevant study
BAJAJ 2009[101]	Incorrect study design
BANERJEE 2008[111]	No multivariate analysis
BARCHETTA 2012[113]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
BEDOGNI 2012[117]	Wrong outcomes; not look at risk factors for NAFLD.
BELLENTANI 2010[121]	Systematic review: incorrect methodology
BEYMER 2003[123]	Adult study. Predictors of NASH/fibrosis: cross-sectional study adjusted multivariate analysis for <3 of our pre-specified confounders.

Reference	Reason for exclusion
BHALA 2013[125]	Narrative review
BHAT 2013[126]	No multivariate analysis
BI 2014[128]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
BLACK 2014[131]	Wrong study design: cross-sectional
BOOKMAN 2006[134]	Irrelevant study
BOOTH 2008[135]	No multivariate analysis
BOYRAZ 2014[141]	Irrelevant study
BOZA 2005[142]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
BOZZETTO 2011[143]	No multivariate analysis
BREA 2005[144]	Irrelevant study
BRIL 2015	Irrelevant study
BRZOZOWSKA 2009[149]	Irrelevant study
BRUNO 2014[147]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
BUGIANESI 2004[152]	Adults study. Predictors NASH/fibrosis: cross-sectional study adjusted multivariate analysis for <3 of our pre-specified confounders.
CABALLERIA 2010[157]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
CAI 2014[159]	Irrelevant study
CABALLERIA 2008[156]	Study protocol
CALANNA 2014[160]	Wrong study design: cross-sectional
CAMPAS 2008[166]	Irrelevant study
CATENA 2013A[176]	Irrelevant study
CHAN 2004[181]	Results not clearly stated in study
CHANG 2009[188]	No multivariate analysis
CHEAH 2013[192]	No multivariate analysis
CHEN 2006A [193]	Unclear multivariate analysis
CHEN 2008D[197]	Metabolic syndrome combined
CHENG 2013A[198]	No multivariate analysis
CHITTURI 2002[202]	Not looking at risk factors
CHUNG 2015A	Wrong study design: cross-sectional
CHUNG 2015B	Wrong study design: cross-sectional
CIBA 2007[209]	No multivariate analysis
CHEN 2007[194]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
CHOUDHARY 2015[206]	Irrelevant study
COLAK 2013A [214]	No multivariate analysis
COLICCHIO 2005[217]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
CONSTANTINESCU 2006[218]	Incorrect Study design
CORDEIRO 2013[221]	No multivariate analysis
CORTEZPINTO 1999	No multivariate analysis

Reference	Reason for exclusion
DADAMO 2010[230]	Irrelevant study
DAI 2009[232]	Not NAFLD
DAS 2010[234]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
DASSANAYAKE 2009[237]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
DESILVA 2006[246]	No multivariate analysis
DEY 2013[255]	No multivariate analysis
DONATI 2004[256]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
DUNN 2013[263]	Irrelevant study
ELKARAKSY 2011[276]	Wrong study design: cross-sectional (predictors of NAFLD)
EL-KOOFY 2012[277]	No multivariate analysis and irrelevant study
FALLO 2008[286]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
FAN 2005[290]	Irrelevant study
FAN 2005A[289]	Not NAFLD
FAN 2007A[287]	Irrelevant study
FASSIO 2004[294]	No multivariate analysis
FRACANZANI 2008[319]	Irrelevant study (looking at whom to liver biopsy)
FRANCQUE 2011[321]	No multivariate analysis
FERNANDES 2010[301]	Irrelevant study (looking at gender differences in NAFLD)
FERRIERA 2010 [304]	No multivariate analysis
FAN 2007C[288]	Incorrect population and no multivariate analysis
FEIJO 2013[297]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
FIERBINTEANUBRATICEVICI 2002[307]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
FIERBINTEANUBRATICEVICI 2011[306]	Adults study. Predictors of NASH/fibrosis: cross-sectional study adjusted multivariate analysis for <3 of our pre-specified confounders.
FINUCANE 2008[309]	Results not clearly stated in study
FINUACANE 2014[310]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
FOSTER 2013[316]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
FOTBOLCU 2010[317]	No multivariate analysis
FRACANZANI 2011[320]	Each risk factor data has been split into multiple categories, rather than giving an overall result.
FRANCQUE 2011[322]	Incorrect population
FRANTZIDES 2004[325]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
FRIISLIBY 2004[330]	Not looking at risk factors
FRITH 2009[331]	No multivariate analysis
FU 2011[332]	Irrelevant study
FUYAN 2013[334]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)

Reference	Reason for exclusion
GABA 2012[335]	No multivariate analysis
GAIANI 2009[337]	No multivariate analysis
GERBER 2012[346]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
GIANOTTI 2014[350]	No multivariate analysis
GOKCE 2013[357]	Not looking at risk factors for NAFLD.
GOLAND 2006[358]	Unclear results
GUIDORIZZI DE SIQUEIRA 2005[367]	No multivariate analysis
GUPTA 2011[374]	Irrelevant study: looking at prevalence of NAFLD
GUPTE 2004[375]	No multivariate analysis
GHAMARCHEHREH 2012[348]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
GHAMARCHEHREH 2013[347]	Wrong study design: cross-sectional (predictors of NAFLD)
GHAMARCHEHREH 2013A [349]	Incorrect population
GOBATO 2014[353]	Wrong study design: cross-sectional (predictors of NAFLD)
GOH 2013[356]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
GRAHAM 2009[360]	No multivariate analysis
GROTTICLEMENTE 2013[364]	Wrong study design: cross-sectional (predictors of NAFLD)
GUNJI 2010[373]	Incorrect population
HAENTJENS 2009[377]	No relevant risk factors
HARRISON 2008[398]	No multivariate analysis
HAMAGUCHI 2005[389]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
HAMAGUCHI 2012[390]	No multivariate analysis
HAMAGUCHI 2012A[388]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
HARNOIS 2006[394]	Unclear multivariate analysis
HE 2011[413]	No multivariate analysis
HEIANZA 2014[415]	Not look at RFs for NAFLD
HICKMAN 2008[421]	No multivariate analysis
HOLTERMAN 2013[427]	No multivariate analysis
HOSSEINI 2011[430]	Inadequate multivariate analysis
HOU 2011[431]	Irrelevant study
HSIAO 2004[435]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
HSIAO 2007[434]	Irrelevant study
HSIAO 2013[433]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
HU 2012[436]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
HUNG 2013B[440]	Inadequate multivariate analysis (adjusted for <3 key confounders)
IACOBELLIS 2014[446]	Inadequate multivariate analysis (adjusted for <3 key confounders)
IMAMURA 2008[451]	Incorrect population

Reference	Reason for exclusion
IMHOF 2007[452]	Irrelevant study
INABE 2012[453]	No multivariate analysis
ISHIBASHI 2008[456]	No multivariate analysis
JAGER 2015[460]	Wrong study design: cross-sectional
JAMALI 2008[462]	Incorrect population
JIANG 2014A[469]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
JIANG 2014B[467]	Irrelevant study
JIMBA 2005[470]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
JU 2013[480]	Inadequate multivariate analysis (adjusted for <3 key confounders)
JUN 2008[482]	Inadequate multivariate analysis (adjusted for <3 key confounders)
JUNG 2014A[485]	Irrelevant study (does not look at risk of firosis in NASH population)
KAMAL 2013[490]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KANTARCEKEN 2007[492]	Results not presented
KASHYAP 2009[496]	Adult study. Predictors of NASH/fibrosis: cross-sectional study adjusted multivariate analysis for <3 of our pre-specified confounders.
KELISHADI 2009A[501]	Wrong study design: cross-sectional (predictors of NAFLD)
KIM 2004[510]	Adult study. Predictors of NAFLD: wrong study design, cros-sectional not cohort.
KIM 2005[511]	No relevant risk factors analysed
KIM 2010F[512]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KIM 2011D [516]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KIM 2013O[515]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KIMURA 2011[519]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KIREL 2012[521]	No multivariate analysis
KIROUSKI 2010[522]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KLEINER 2014[524]	Not look at risk factors for NAFLD
KODHELAJ 2014[527]	Wrong study design: cross-sectional (predictors of NAFLD)
KOEHLER 2012[528]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KOGISO 2007[530]	Mixed population of adults and children and has not stratified /separated the multivariate results by age-group. (predictors of NAFLD)
KOJIMA 2003[531]	Results not fully given, cannot analyse
KOSMALSKI 2013[534]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KOTRONEN 2008[536]	Irrelevant study
KOTRONEN 2009A[535]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
KOTRONEN 2010[538]	Compares NAFLD vs. AFLD
KRISHNAN 2011[541]	No multivariate analysis

Reference	Reason for exclusion
KRUGER 2010[542]	No multivariate analysis
KWON 2012A[550]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
LAI 2002[552]	Not specifically NAFLD.
LAI 2008[551]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
LANKARANI 2013[553]	No multivariate analysis
LATEA 2013[556]	No multivariate analysis
LAWLOR 2014[562]	Wrong study design: cross-sectional (predictors of NAFLD)
LAU 2010[557]	Irrelevant study
LAZO 2013[565]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
LEE 2006[573]	No multivariate analysis
LEE 2008[580]	Incorrect study design
LEE 2009A[571]	No multivariate analysis
LEE 2010[568]	Not relevant study to review question
LEITE 2009[581]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
LI 2009[584]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
LOVEOSBORNE 2008[600]	No multivariate analysis
LUXMI 2008[606]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
MA 2009[608]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
MACHADO 2006[612]	Systematic review: incorrect methodology
MADDAH 2012[616]	No multivariate analysis
MADAN 2012[613]	Narrative review
MAJID 2013[621]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
MANTOVANI 2012[628]	Irrelevant study
MANTOVANI 2015[629]	Inadequate multivariate analysis (adjusted for <3 key confounders)
MARCHESINI 1999[630]	No multivariate analysis
MARTINEZALVARADO 2014[636]	Wrong study design: cross-sectional
MIYAKE 2013A[661]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
MOHAN 2009[662]	Inadequate multivariate analysis (adjusted for <3 key confounders)
MONTEIRO 2014[664]	No multivariate analysis
NADEAU 2005[681]	No relevant outcomes
NAKAO 2002[685]	Inadequate multivariate analysis (adjusted for <3 key confounders)
NAVARRO-JARABO 2013[691]	Incorrect population (unclear whether results given for population with NAFLD, NASH, fibrosis or all of these combined)
NEUSCHWANDERTETRI 2010[695]	Adults study. Predictors of NASH/fibrosis: cross-sectional study but details of results are not provided for multivariate analysis (no effect sizes provided).

Reference	Reason for exclusion
NOBILI 2009A[703]	Irrelevant study
ONG 2005[715]	Unclear multivariate analysis
OSTOVANEH 2015[724]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
OZKOL 2010[728]	Incorrect population
PACIFICO 2014[730]	Irrelevant study
PARK 2004A[745]	Unclear multivariate analysis
PARK 2007[748]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
PARK 2007A[744]	Irrelevant study
PARK 2008B[742]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
PICKHARDT 2014[765]	Irrelevant study
POREPA 2010[773]	Incorrect outcome (cirrhosis and liver failure)
PORTILLO 2015[774]	No multivariate analysis
PRASHANTH 2009[783]	Irrelevant study
PULJIZ 2010[789]	No multivariate analysis
QARI 2005[791]	No multivariate analysis
QU 2012[793]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
QUIROSTEJEIRA 2007[794]	Inadequate multivariate analysis
RADU 2008[796]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
RASZEJAWYSZOMIRSKA 2010[802]	Irrelevant study
RASZEJAWYSZOMIRSKA 2011[801]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
REHA 2014[808]	No multivariate analysis
REHM 2014[809]	Results not clearly stated in study
RIQUELME 2009[814]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
RODRIGUEZ-HERNANDEZ 2008[816]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SAKI 2014[824]	Irrelevant study
SANCHES 2014[828]	Inadequate multivariate analysis (adjusted for <3 key confounders)
SANAL 2011[827]	No multivariate analysis
SATHIARAJ 2011[842]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SANDBOGE 2013[829]	Irrelevant risk factors
SANYAL 2009[836]	No multivariate analysis
SAVVIDOU 2009[844]	Irrelevant covariates adjusted for in multivariate analysis
SCHLIESKE 2015[847]	Irrelevant study: not looking at risk factors of NAFLD
SCHWIMMER 2008[852]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SEO 2012[856]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SHARIFIAN 2012[864]	Wrong study design for adult population: cross-sectional (predictors of

Reference	Reason for exclusion
	NAFLD)
SHEN 2003[869]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SHEN 2014F	Wrong study design: cross-sectional
SHIGA 2009[874]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SILVEIRA 2013[876]	No relevant multivariate analysis
SIMA 2014[877]	Wrong study design: cross-sectional
SIMONEN 2011[881]	Systematic review: incorrect methodology
SINGH 2008[882]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SIGNH 2013[883]	No multivariate analysis
SINN 2012[886]	Irrelevant study
SMITS 2013[890]	Irrelevant study
SOBHONSLIDSUK 2007[891]	No multivariate analysis
SOLGA[896]	No multivariate analysis
SONG 2008[898]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SORESI 2013[902]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SORRENTINO 2004A[903]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SORRENTINO 2010A [904]	Incorrect outcome
SOUZA 2012[905]	Systematic review: incorrect methodology
STEPANOVA 2010[916]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
SU 2006[922]	No multivariate analysis
SUNG 2014[934]	Incorrect population
SUNG 2014A[930]	Wrong Study design: cross-sectional
SUOMELA 2015[936]	Incorrect population: NAFLD at baseline
SYN 2008[938]	No multivariate analysis
TARANTINO 2008[943]	No multivariate analysis
TASEER 2009[954]	No multivariate analysis
TOMINAGA 1995[966]	No multivariate analysis
TOMIZAWA 2014[968]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
TOTAMAHARAJ 2014[972]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
TROJAK 2013[975]	Irrelevant study
TSAI 2008[977]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
TSANG 2006[978]	Adult study. Predictors of NASH/fibrosis: cross-sectional study but none of our pre-specified prognostic factors were looked at in the analysis.
TSUNETO 2010[979]	Wrong population: unclear if NAFLD as just says fatty liver, and does not specify if they included or excluded people with high alcohol consumption. Very specific population – not applicable to the general UK population (Nagasaki atomic bomb survivors).

Reference	Reason for exclusion
TSURUTA 2010[980]	Unclear results
TUNG 2011[981]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
VALANTINAS 2012[990]	No multivariate analysis
VASUNTA 2012[997]	No relevant risk factors reported
VERNON 2011[999]	Systematic review: incorrect methodology
VINODH 2013[1004]	No multivariate analysis
WANG 2007[1024]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
WANG 2010B[1023]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
WANG 2014A[1025]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
WANG 2012[1016]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
WANG 2012A[1021]	Irrelevant study: not looking at risk factors of NAFLD
WANG 2013A[1026]	Unclear multivariate analysis
WANG 2013F[1022]	No multivariate analysis
WANG 2014A[1025]	Incorrect study design
WICKLOW 2012[1029]	Irrelevant study: not looking at risk factors of NAFLD
WONG 2004[1035]	No multivariate analysis
WONG 2008A[1031]	Irrelevant study: not looking at risk factors of NAFLD
WONG 2012B[1043]	No multivariate analysis
WONG 2013B[1033]	Incorrect outcome
WU 2015A[1048]	Incorrect population: part of the population has NAFLD at baseline.
XIAO 2014[1050]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
YAMADA 2010A[1055]	Irrelevant study
YAN 2013A[1057]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
YILMAZ 2014A[1065]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
YING 2012[1067]	Unclear if multivariate analysis carried out
YOUNOSSI 2013[1075]	Irrelevant study: not looking at risk factors of NAFLD
YUE 2013[1077]	Irrelevant study: not looking at risk factors of NAFLD
YUN 2009B	Irrelevant study: not looking at risk factors of NAFLD
ZAKI 2013[1078]	No multivariate analysis
ZELBERSAGI 2006[1086]	Wrong study design for adult population: cross-sectional (predictors of NAFLD)
ZELBERSAGI 2012A[1085]	Adult study. Prospective cohort study but has not adjusted the multivariate analysis for ≥3 of our pre-specified confounders (predictors of NAFLD)
ZELBERSAGI 2014[1088]	Adult study. Prospective cohort study but has not adjusted the multivariate analysis for ≥3 of our pre-specified confounders (predictors of NAFLD)
ZHANG 2015B[1092]	Adjusted for <3 confounders

Reference	Reason for exclusion
ZHENG 2012[1093]	No multivariate analysis
ZHOU 2007[1095]	Incorrect population
ZHOU 2012[1094]	prospective cohort study in adults, but data combined in analysis for patients with no NAFLD at baseline who went on to develop NAFLD + patients with NAFLD at baseline who became more severe
ZIMMERMANN 2015[1097]	Adjusted for <3 confounders
ZUEFF 2012[1098]	Incorrect population: polycystic ovary syndrome.

M.2 Diagnosis of NAFLD

Table 46: Studies excluded from the clinical review for diagnosis of NAFLD

Reference	Reason for exclusion
Abrigo 2013[11]	Insufficient data
Abrigo 2014[12]	Incorrect study design
Adani 2006[18]	Population does not match protocol
Al-Busafi 2012[29]	Index test does not match protocol
Alkhouri 2014[45]	Insufficient data
Alonte 2014[50]	Insufficient data
Alquiroz 2014[52]	Index test and reference standard do not match protocol
Alshaalan 2013[53]	Population does not match protocol
Andre 2015 [61]	Reference standard does not match protocol
Arteaga 2014 [83]	Not in English
Awai 2014[93]	Population does not match protocol
Banerjee 2014[110]	Population does not match protocol
Bazick 2015 [115]	Population does not match protocol
Beaugrand 2010[116]	Population does not match protocol
Besutti 2010[122]	Insufficient data
Bhatnagar 2012[127]	Incorrect study design
Bi 2013[129]	Incorrect study design
Bohte 2011[132]	Incorrect study design
Bonekamp 2011[133]	Incorrect study design
Borges 2013[136]	Incorrect study design
Bril 2013[145]	Insufficient data
Bril 2015 [146]	Incorrect study design and population does not match protocol
Brunt 2011[148]	Index test does not match protocol
Campion 2014[165]	Index test does not match protocol
Casey 2010[173]	Index test does not match protocol
Castera 2013[174]	Incorrect study design
Caturelli 1992[177]	Incorrect study design
Chan 2014 [185]	Population does not match protocol
Chiang 2014[200]	Population does not match protocol
Cichy 2012[211]	Reference standard does not match protocol
Cotler 2007[225]	Insufficient data
Cui 2015 [228]	Population does not match protocol

Reference	Reason for exclusion
d'Assignies 2009[231]	Population does not match protocol
Debongnie 1981[248]	Outcome does not match protocol
de Ledinghen 2014[240]	Conference abstract
de Ledinghen 2014[247]	Conference abstract
de Ledinghen 2014[241]	Insufficient data
El-Koofy 2012[277]	Incorrect study design
Ergun 1999[279]	Incorrect study design
Estep 2013[283]	Insufficient data
Ferraioli 2013[302]	Conference abstract
Festi 2013[305]	Incorrect study design
Fischer 2010[312]	Insufficient data
Fischer 2012[311]	Insufficient data
Fishbein 2005[313]	Insufficient data
Francque 2010[323]	Insufficient data
Francque 2012[324]	Index test does not match protocol
Friedrich-Rust 2010[329]	Insufficient data
Fuyan 2013[334]	Reference standard does not match protocol
Galimberti 2015 [338]	Reference standard does not match protocol
Georgoff 2012[345]	Insufficient data
Godfrey 2012[354]	Outcome does not match protocol
Graif 2000[361]	Incorrect study design
Grattagliano 2013[362]	Incorrect study design
Guaraldi 2012[365]	Insufficient data
Gul 2010[368]	Index test does not match protocol
Hamaguchi 2007[387]	Insufficient data
Hashimoto 2012[403]	Incorrect study design
Hegazy 2013[414]	Insufficient data
Henninger 2013[416]	Incorrect study design
Hernaez 2011[419]	Incorrect study design
Hirche 2007[424]	Incorrect study design
Hollebecque 2010[425]	Insufficient data
House 2013[432]	Insufficient data
Hultcrantz 1993[439]	Insufficient data
Husain 2014[441]	Reference standard does not match protocol
Hussain 2010[442]	Population does not match protocol
Hwang 2014[444]	Incorrect study design
Icer 2012[447]	Incorrect study design
Iijima 2007[449]	Incorrect study design
Ismail 2014[457]	Incorrect study design
Jeong 2005[466]	Reference standard does not match protocol
Jiang 2013[468]	Reference standard does not match protocol
Joseph 1991[478]	Incorrect study design
Joy 2003[479]	Incorrect study design

Reference	Reason for exclusion
Jun 2013 [483]	Insufficient data
Kallwitz 2009[488]	Conference abstract
Khov 2014[506]	Incorrect study design
Kikuchi 2014[507]	Reference standard does not match protocol
Kligman 2011[525]	Insufficient data
Korpraphong 2015 [533]	Outcome does not match protocol
Kotronen 2009[537]	Reference standard does not match protocol
Kotronen 2009[535]	Reference standard does not match protocol
Kumar 2013[546]	Population does not match protocol
Lazar 2012[563]	Insufficient data
Lee 2010[568]	Incorrect study design
Lee 2014[574]	Incorrect study design
Lupsor 2012[603]	Conference abstract
Ma 2009[607]	Incorrect study design
Marks 1997[631]	Insufficient data
Maruzzelli 2014[637]	Insufficient data
Maximos 2014[643]	Insufficient data
Mcpherson 2009[651]	Insufficient data
Mcpherson 2009[648]	Insufficient data
Meffert 2014[652]	Incorrect study design
Mehta 2008[653]	Incorrect study design
Mi 2015[656]	Reference standard does not match protocol
Minhas 2012[660]	Incorrect study design
Mottin 2004[674]	Incorrect study design
Nascimbeni 2014[687]	Insufficient data
Naveau 2012[693]	Insufficient data
Naveau 2014 [692]	Outcome does not match protocol
Nobili 2011[699]	Incorrect study design
Osawa 1996[723]	Reference standard does not match protocol
Otgonsuren 2014[725]	Incorrect study design
Pacifico 2010[732]	Insufficient data
Pais 2009[735]	Incorrect study design
Parente 2014[741]	Insufficient data
Patwardhan 2012[753]	Insufficient data
Pearce 2013[754]	Incorrect study design
Pimentel 2010[767]	Index test does not match protocol
Pineda-Bonilla 2012[768]	Index test does not match protocol
Piperno 2013[769]	Insufficient data
Pirvulescu 2012[770]	Incorrect study design
Poynard 2012[782]	Insufficient data
Pulzi 2011[790]	Index test does not match protocol
Qayyum 2009[792]	Incorrect study design
Ramirez 2010[799]	Index test does not match protocol

Reference	Reason for exclusion
Ratziu 2006[806]	Index test does not match protocol
Rinella 2003[813]	Incorrect study design
Roldan-Valadez 2009[817]	Insufficient data
Sasso 2010[840]	Conference abstract
Schuchmann 2007[848]	Population does not match protocol
Sevastianova 2010[859]	Population does not match protocol
Shi 2014[870]	Incorrect study design
Simentalmendia 2012[879]	Index test does not match protocol
Simo 2012[880]	Index test does not match protocol
Sirli 2014 [887]	Index test does not match protocol
Sohail 2013[895]	Incorrect study design
Sporea 2009[910]	Incorrect study design
Steadman 2013 [915]	Incorrect study design
Tazawa 1997[955]	Reference standard does not match protocol
Vajro 2012[988]	Incorrect study design
Verrijken 2009[1000]	Insufficient data
Vitturi 2015 [1005]	Reference standard does not match protocol
von Herbay 2001[1009]	Incorrect study design
Vuppalanchi 2007[1012]	Insufficient data
Wong 2012[1032]	Insufficient data
Wu 2012[1047]	Incorrect study design
Wu 2014[1045]	Incorrect study design
Yeh 2005[1060]	Insufficient data
Yilmaz 2014[1066]	Insufficient data
Yoon 2015 [1072]	Index test does not match protocol
Younossi 2013[1075]	Reference standard does not match protocol

M.3 Diagnosing the severity of NAFLD

Table 47: Studies excluded from the clinical review for diagnosing the severity of NAFLD

Study	Exclusion reason
Akyuz 2014[28]	Insufficient data
Alam 2013[33]	Insufficient data
Alkhouri 2011[41]	Insufficient data
Alkhouri 2013[44]	Index test and outcome do not match protocol
Alkhouri 2014[43]	Insufficient data
Bril 2015 [146]	Incorrect study design
Bulow 2013[153]	Incorrect reference standard
Cales 2008[164]	Incorrect population
Cales 2010[163]	Insufficient data
Caner 2014 [167]	Incorrect reference standard
Cao 2013[169]	Insufficient data
Carter-Kent 2009[171]	Insufficient data

Study	Exclusion reason
Chan 2012[182]	Included as Shen 2012
Chandok 2012[186]	Insufficient data
Chen 2011[195]	Index test and outcome do not match protocol
Chen 2014[196]	Incorrect study design
Chowdhury 2013[207]	Index test and outcome do not match protocol
d'Assignies 2009[231]	Population does not match protocol
Demir 2013[251]	Already included as Demir 2013B
Dowman 2011[258]	Incorrect study design
Elias 2009[278]	Insufficient data
Fan 2012[291]	Not in English
Fitzpatrick 2010[314]	Insufficient data
Francque 2012[324]	Insufficient data
Friedrich-Rust 2010[327]	Insufficient data
Friedrich-Rust 2012[328]	Insufficient data
Gaia 2011[336]	Population does not match protocol
Harrison 2008[398]	Insufficient data
Kalra 2009[489]	Index test and outcome do not match protocol
Kowdley 2012[539]	Insufficient data
Kwok 2014[548]	Incorrect study design
Lebensztejn 2011[567]	Index test and outcome do not match protocol
Li 2012[586]	Not in English
Loaeza-del-Castillo 2008 [595]	Incorrect reference standard
Maher 2015	Population does not match protocol
Mansoor 2015 [627]	Insufficient data
McPherson 2013[647]	Incorrect study design. Protocol-relevant evidence included as McPherson 2010
Musso 2011 [677]	Incorrect study design
Naveau 2014 [692]	Population does not match protocol
Noren 2008 [706]	Population does not match protocol
Noureddin 2013 [707]	Incorrect study design
Ochi 2012 [711]	Index test does not match protocol
Orlacchio 2012 [720]	Index test does not match protocol
Osaki 2010 [722]	Population does not match protocol
Permutt 2012 [760]	Index test and outcome do not match protocol
Petta 2015 [763]	Incorrect study design and insufficient data
Poynard 2005 [781]	Population does not match protocol
Poynard 2006 [780]	Insufficient data
Poynard 2007 [777]	Incorrect study design
Poynard 2008 [778]	Incorrect study design
Poynard 2012 [779]	Incorrect study design
Saadeh 2002 [822]	Index test and outcome do not match protocol
Sebastiani 2011 [855]	Incorrect reference standard
Sowa 2013 [906]	Index test and outcome do not match protocol

Study	Exclusion reason
Sporea 2013 [909]	Incorrect reference standard
Steadman 2013 [915]	Incorrect study design
Subasi 2015 [923]	Insufficient data
Tamano 2012 [939]	Incorrect reference standard
Tang 2013 [940]	Index test and outcome do not match protocol
Tapper 2014 [942]	Incorrect reference standard
Tomita 2008 [967]	Index test and outcome do not match protocol
Uslusoy 2009 [985]	Index test and outcome do not match protocol
Wieckowska 2006 [1030]	Population does not match protocol
Yang 2012 [1058]	Index test and outcome do not match protocol
Yilmaz 2011 [1064]	Insufficient data
Younossi 2008 [1074]	Incorrect reference standard

M.4 Monitoring NAFLD progression

Table 48: Studies excluded from the clinical review of monitoring NAFLD progression

Reference	Reason for exclusion
Argo 2009 [75]	Indirect population. Previous part of a treatment trial.
Bhala 2011[124]	Indirect outcomes, no measurements of fibrosis.
Caldwell 2009[162]	Not possible to extract data from given information on baseline values although described in the methods
Charatcharoenwitthaya 2012[190]	Not possible to extract data from given information on repeat biopsy values although described in the methods
Dam-Larsen 2005[233]	No relevant outcomes and does not match review question
Haflidadottir 2014[378]	No follow-up measurement of fibrosis
Mindikoglu 2006[659]	An indirect population- comorbid hepatitis C in liver transplant people on immunosupression
Onnerhag 2014[718]	Indirect outcomes- non established scale used, and no information on grading at follow-up reported
Pais 2011[734]	Subset of larger included study
Park 2005[746]	No relevant outcomes and does not match review question
Powell 1990[776]	Indirect population- included cirrhotic people.
Ratziu 2000[803]	Indirect outcome- graded on the Metavir scale.
Singh 2014[884]	Systematic review that does not match review question
Sung 2013 [928]	Indirect population- comorbid alcohol use
Suzuki 2013	Outcome indirect- used transient elastrography scans to diagnose and monitor fibrosis
Zhou 2012[1094]	Outcome indirect- used ultrasound scans to diagnose and monitor fibrosis

M.5 Extra-hepatic conditions

Table 49: Studies excluded from the clinical review of extra-hepatic conditions

Reference	Reason for exclusion
Adams 2005[14]	Incorrect study design

Reference	Reason for exclusion
Adams 2009[15]	Analysis does not match protocol (key confounders not included in analysis)
Akiyama 2009 [26]	Prognostic variable does not match protocol
Alp 2013 [51]	Incorrect study design
Ampuero 2015 [59]	Incorrect study design
Angulo 2013 [65]	Outcome does not match protocol
Arase 2009a [70]	Prognostic variable does not match protocol
Arase 2011 [71]	Prognostic variable does not match protocol
Armstrong 2014 [78]	Incorrect study design
Arslan 2013a [82]	Incorrect study design
Assy 2010 [85]	Incorrect study design
Aygun 2008 [94]	Incorrect study design
Baba 2007 [96]	Population does not match protocol
Baktir 2015 [103]	Incorrect study design
Baloseanu 2012 [108]	Incorrect study design
Baranova 2011 [112]	Incorrect study design
Bhala 2011 [124]	Extra-hepatic condition does not match protocol
Brea 2005 [144]	Incorrect study design
Brzozowska 2009 [149]	Incorrect study design
Cai 2015 [158]	Incorrect study design
Choi 2013b [204]	Prognostic variable does not match protocol
Colak 2012 [215]	Incorrect study design
Colak 2013 [216]	Incorrect study design
Corey 2014a [222]	Incorrect study design
Demircioglu 2008 [253]	Incorrect study design
Efe 2014 [270]	Incorrect study design
Ekstedt 2006 [273]	Incorrect study design
Fargion 2014 [292]	Incorrect study design
Fintini 2014 [308]	Incorrect study design
Fotbolcu 2010 [317]	Incorrect study design
Fotbolcu 2010b [318]	Incorrect study design
Fracanzani 2008 [319]	Incorrect study design
Friis-Liby 2004 [330]	Incorrect study design
Goland 2006 [358]	Incorrect study design
Guidorizzi de Siqueira 2005 [367]	Analysis does not match protocol
Guleria 2013 [369]	Incorrect study design
Hallsworth 2013 [382]	Incorrect study design
Hamaguchi 2007 [386]	Analysis does not match protocol (key confounder not included in analysis)
Hanley 2004 [392]	Population does not match protocol
Hanley 2005 [393]	Population does not match protocol
Hatziagelaki 2012 [406]	Incorrect study design
Haukeland 2012 [408]	Incorrect study design
Holt 2006 [426]	Outcome does not match protocol

Reference	Reason for exclusion
Inoue 2013 [454]	Outcome does not match protocol
Jablonski 2013 [459]	Outcome does not match protocol
Jin 2005 [471]	Incorrect study design
Jung 2014a [485]	Incorrect study design
Kantartzis 2008 [494]	Incorrect study design
Kim 2014f [513]	Incorrect study design
Kimura 2011 [519]	Incorrect study design
Kocabay 2014 [526]	Prognostic variable does not match protocol
Kucukazman 2014 [544]	Incorrect study design
Leach 2014 [566]	Incorrect study design
Li 2015 [585]	Outcome does not match protocol
Liew 2008 [587]	Outcome does not match protocol
Lizardi-Cervera 2007 [594]	Incorrect study design
Lomonaco 2012 [597]	Incorrect study design
Lucero 2011 [601]	Incorrect study design
Machado 2012a [611]	Incorrect study design
Madan 2006 [615]	Incorrect study design
Manchanayake 2011 [623]	Incorrect study design
Manco 2009 [625]	Incorrect study design
Manco 2010 [624]	Incorrect study design
Miksztowicz 2012 [658]	Incorrect study design
Musso 2013a [676]	Incorrect study design
Musso 2014 [678]	Incorrect study design
Nahandi 2014 [682]	Incorrect study design
Oni 2013 [716]	Incorrect study design
Perazzo 2014a [757]	Incorrect study design
Picardi 2008 [764]	Incorrect study design
Rafiq 2009 [797]	Outcome does not match protocol
Sargin 2003 [837]	Incorrect study design
Schulz 2015 [849]	Outcome does not match protocol
Schwimmer 2003 [850]	Outcome does not match protocol
Sinn 2012 [886]	Incorrect study design
Soderberg 2010 [892]	Outcome does not match protocol
Sookoian 2008 [900]	Incorrect study design
Sorensen 2003 [901]	Incorrect study design
Stadlmayr 2011 [914]	Incorrect study design
Stepanova 2012a [917]	Re-analysis of same population as already included study Lazo 2011
Sung 2009a [933]	Incorrect study design
Sung 2011 [932]	Prognostic variable does not match protocol
Sung 2012a [929]	Prognostic variable does not match protocol
Sung 2012b [935]	Incorrect study design
Sung 2013 [928]	Incorrect population
Tarantino 2014a [944]	Incorrect study design

Reference	Reason for exclusion
Targher 2005 [947]	Duplicate population of Targher 2007. Supplementary data added to evidence table
Targher 2006a [945]	Incorrect study design
Targher 2006c [946]	Incorrect study design
Targher 2008b [948]	Incorrect study design
Targher 2013b [953]	Incorrect study design
Treeprasertsuk 2012 [973]	Inadequate outcome reporting (insufficient information provided for inclusion)
Van Wagner 2015 [996]	Incorrect study design
Vernon 2011 [999]	Incorrect study design
Wang 2009 [1015]	Incorrect study design
Wong 2010 [1034]	Outcome does not match protocol
Wong 2011a [1040]	Incorrect study design
Yasui 2011a [1059]	Incorrect study design
You 2015 [1073]	Incorrect population

M.6 Weight reduction interventions

Table 50: Studies excluded from the clinical review of weight reduction interventions

Study	Exclusion reason
Abenavoli 2013[8]	Conference abstract
Ahmad 2012[19]	Conference abstracts
Al-gayyar 2012[30]	No relevant outcomes
Alisi 2012[39]	Incorrect interventions
Al-jiffri 2013[32]	Incorrect interventions
Aller 2014[47]	Inappropriate comparison
Arefhosseini 2011[73]	Inappropriate comparison
Athyros 2013[89]	Study protocol. Incorrect interventions
Bellentani 2008[120]	Incorrect interventions
Boyraz 2013[139]	Conference abstract
Buchmiller 1993[150]	Not review population
Buss 2014[155]	Systematic review: methods are not adequate/unclear
Caldwell 2011[161]	Conference abstract
Capanni 2006[170]	RCTs available, prospective cohort excluded
Chachay 2014[179]	Incorrect intervention
Chiu 2014[203]	Systematic review: methods are not adequate/unclear
Chung 2014[208]	Systematic review: methods are not adequate/unclear
Clark 2006[213]	Incorrect interventions
Cruz 2012[227]	Conference abstract
Dasarathy 2015[235]	Incorrect population
De luis 2010[243]	Inappropriate comparison

Ebrahimi-Mameghani 2014[268]	Incorrect intervention
Faghihzadeh 2014[285]	Incorrect intervention
Farhangi 2014[293]	Incorrect intervention
Glass 2015[352]	Incorrect interventions
Hayward 2010[412]	Conference abstract
Hongfang 2014[428]	Systematic review: methods are not adequate/unclear
Janczyk 2013[464]	Study protocol
Johnston 2010[476]	Conference abstract
Jun 2013[481]	Conference abstract
Kani 2014[491]	Incorrect interventions
Kelishadi 2013[502]	Systematic review is not relevant to review question or unclear PICO
Kellow 2014[503]	Systematic review is not relevant to review question or unclear PICO. Systematic review: methods are not adequate/unclear
Lirussi 2007[591]	Systematic review: methods are not adequate/unclear
Lirussi 2007[590]	Systematic review is not relevant to review question or unclear PICO
Ma 2013[609]	Systematic review is not relevant to review question or unclear PICO
Mager 2015[617]	Incorrect intervention
Martin 2013[635]	Conference abstracts
Masterton 2010[639]	Systematic review: methods are not adequate/unclear
Mazokopakis 2014[644]	Incorrect study design
Nabavi 2013[680]	Conference abstract
Papandreou 2008[738]	Incorrect study design
Parker 2011[750]	Conference abstract
Parker 2012[749]	Systematic review is not relevant to review question or unclear PICO
Poustchi 2013[775]	Conference abstract
Ramon-krauel 2013[800]	Inappropriate comparison
Rodriguez-hernandez 2011[815]	Inappropriate comparison
Saab 2014[820]	Systematic review is not relevant to review question or unclear PICO
Sarkhy 2014[838]	Incorrect intervention
Sofi 2010[894]	Incorrect interventions
Somi 2014[897]	Incorrect intervention
St george 2009[912]	Incorrect interventions
Trovato 2015[976]	Incorrect study design
Ueno 1997[983]	Incorrect interventions
Utzschneider 2013[986]	Inappropriate comparison
Vos 2009[1011]	Incorrect interventions
Wang 2003[1020]	Systematic review is not relevant to review question or unclear PICO
Wong 2012[1036]	Conference abstract
Wong 2013[1042]	Incorrect interventions
Zhang 2015[1091]	Incorrect intervention

M.7 Dietary modification and supplements

Table 51: Studies excluded from the clinical review of dietary modification and supplements

Study	Exclusion reason
Abenavoli 2013[8]	Conference abstract
Ahmad 2012[19]	Conference abstracts
Al-gayyar 2012[30]	No relevant outcomes
Alisi 2012[39]	Incorrect interventions
Al-jiffri 2013[32]	Incorrect interventions
Aller 2014[47]	Inappropriate comparison
Arefhosseini 2011[73]	Inappropriate comparison
Athyros 2013[89]	Study protocol. Incorrect interventions
Bellentani 2008[120]	Incorrect interventions
Boyraz 2013[139]	Conference abstract
Boyraz 2015 [140]	Incorrect outcome measurement
Buchmiller 1993[150]	Not review population
Buss 2014 [155]	Systematic review: methods are not adequate/unclear
Caldwell 2011[161]	Conference abstract
Capanni 2006[170]	RCTs available, prospective cohort excluded
Chachay 2014 [179]	Incorrect interventions
Chiu 2014[203]	Systematic review: methods are not adequate/unclear
Chung 2014[208]	Systematic review: methods are not adequate/unclear
Clark 2006[213]	Incorrect interventions
Copaci 2015 [219]	Incorrect study design
Cruz 2012[227]	Conference abstract
Dasarathy 2015 [235]	Incorrect population
De luis 2010[243]	Inappropriate comparison
Ebrahimi-Mameghani 2014 [268]	Incorrect interventions
Faghihzadeh 2014 [285]	Incorrect interventions
Farhangi 2014 [293]	Incorrect interventions
Glass 2015 [352]	Incorrect study design
Hayward 2010[412]	Conference abstract
Hong-Fang 2014 [428]	Systematic review: Incorrect population
Janczyk 2013[464]	Study protocol
Johnston 2010[476]	Conference abstract
Jun 2013[481]	Conference abstract

Kani 2014[491]	Incorrect interventions
Kelishadi 2013[502]	Systematic review is not relevant to review question or unclear PICO
Kellow 2014[503]	Systematic review is not relevant to review question or unclear PICO. Systematic review: methods are not adequate/unclear
Lirussi 2007[591]	Systematic review: methods are not adequate/unclear
Lirussi 2007[590]	Systematic review is not relevant to review question or unclear PICO
Ma 2013[609]	Systematic review is not relevant to review question or unclear PICO
Mager 2015 [617]	Incorrect study design
Martin 2013[635]	Conference abstracts
Masterton 2010 [639]	Incorrect study design
Mazokopakis 2014 [644]	Incorrect study design
McCormick 2015 [646]	Incorrect study design
Nabavi 2013[680]	Conference abstract
Papandreou 2008[738]	Incorrect study design
Parker 2011[750]	Conference abstract
Parker 2012[749]	Systematic review is not relevant to review question or unclear PICO
Poustchi 2013[775]	Conference abstract
Ramon-krauel 2013[800]	Inappropriate comparison
Rodriguez-hernandez 2011[815]	Inappropriate comparison
Saab 2014[820]	Systematic review is not relevant to review question or unclear PICO
Sarkhy 2014 [838]	Incorrect interventions
Sofi 2010[894]	Incorrect interventions
Somi 2014 [897]	Incorrect interventions
St George 2009[912]	Incorrect interventions
Trovato 2015 [976]	Incorrect study design
Ueno 1997[983]	Incorrect interventions
Utzschneider 2013[986]	Inappropriate comparison
Vos 2009[1011]	Incorrect interventions
Wang 2003[1020]	Systematic review is not relevant to review question or unclear PICO
Wong 2012[1036]	Conference abstract
Wong 2013[1042]	Incorrect interventions
Zhang 2015 [1091]	Incorrect interventions

M.8 Exercise interventions

Table 52: Studies excluded from the clinical review of exercise interventions

Study	Exclusion reason

Study	Exclusion reason
Akyuz 2007[27]	Incorrect interventions
Al-jiffri 2013[32]	Incorrect interventions
Bacchi 2013[98]	Inappropriate comparison
Caldwell 2011[161]	Not review population
Chen 2008[197]	Non RCT study (RCTs available)
Cinar 2006[212]	Wrong study type
Cruz 2012[227]	Incorrect interventions
Davis 2011[238]	Not review population
De piano 2012[245]	Inappropriate comparison
Drexel 2013[259]	Incorrect interventions
Dwyer 2012[267]	Incorrect interventions
Hallsworth 2013[382]	No outcomes of interest
Hasson 2012[405]	Not review population
Hayward 2010[412]	Incorrect interventions
Jakovljevic 2013[461]	No outcomes of interest
Jin 2012[473]	Wrong study design
Johnson 2009[475]	Less than minimum duration
Kantartzis 2009[493]	Wrong study design
Kawaguchi 2011[498]	Incorrect interventions
Keating 2012[500]	Systematic review: quality assessment is inadequate
Khaoshbaten 2013[504]	Incorrect interventions
Koot 2011[532]	Incorrect interventions
Larson-meyer 2008[554]	Incorrect interventions
Lee 2012[576]	Not review population
Lee 2013[577]	Not review population
Lee 2013[572]	Not review population
Lesser 2012[582]	Not review population
Liu 2014[592]	Wrong study type
Magkos 2010[618]	Wrong study type
Masuo 2012[640]	Not review population
Mazzotti 2014[645]	Incorrect interventions
Monteiro 2012[665]	Systematic review is not relevant to review question or unclear PICO
Montesi 2013[666]	Incorrect interventions
Moscatiello 2011[672]	Incorrect interventions
Nikroo 2011[696]	Not review population
Nobili 2008[704]	Incorrect interventions
Oza 2009[726]	Inappropriate comparison
Pacifico 2013[729]	Incorrect study design
Park 1995[743]	Incorrect study design
Parker 2011[750]	Incorrect interventions
Peng 2011[755]	Systematic review is not relevant to review question or unclear PICO
Perseghin 2007[761]	Not review population. Incorrect interventions
Promrat 2010[786]	Incorrect interventions

Study	Exclusion reason
Pugh 2011[787]	Wrong study type
Rafiq 2008[798]	Wrong study type
Reinehr 2009[810]	Incorrect interventions
Saad 2010[821]	Incorrect interventions
Saely 2014[823]	Not review population
Santiprabhob 2012[830]	Incorrect interventions
Scaglioni 2013[845]	Incorrect study design
Schafer 2007[846]	Not review population
Serin 2002[858]	Inappropriate comparison
Shah 2009[862]	Incorrect interventions
Sima 2014[878]	Incorrect interventions
Slentz 2011[888]	Not review population
Smith 2010[889]	No outcomes of interest
Sreenivasa baba 2006[911]	Not review population
St george 2009[913]	Incorrect interventions
St george 2009[912]	Incorrect interventions
Stewart 2008[919]	Not review population
Straznicky 2012[920]	Incorrect interventions
Suzuki 2005[937]	Wrong study type
Thoma 2012[960]	Systematic review: quality assessment is inadequate
Thoma 2012[957]	Systematic review: methods are not adequate/unclear
Tock 2006[964]	Incorrect interventions. Inappropriate comparison
Ueno 1997[983]	Incorrect interventions
Van der heijden 2010[991]	Not review population
Vilar 2008[1002]	Incorrect interventions
Vilar gomez 2009[1001]	Incorrect interventions
Wang 2003[1020]	Systematic review is not relevant to review question or unclear PICO
Wang 2008[1017]	Incorrect interventions
Whitsett 2015 [1028]	Systematic review: including studies that do not match our protocol
Xiao 2013[1049]	Systematic review: methods are not adequate/unclear

M.9 Lifestyle modification

Table 53: Studies excluded from the clinical review of lifestyle modification

Study	Exclusion reason
Albu 2010[36]	Not review population
Alisi 2012[39]	Systematic review: methods are not adequate/unclear
Anon 2013[1]	Narrative review
Athyros 2013[89]	Incorrect interventions. Study protocol
Balducci 2015[105]	Incorrect population
Bellentani 2008[120]	Systematic review is not relevant to review question or unclear PICO
Boyraz 2013[139]	Conference abstract
Caldwell 2011[161]	Conference abstract

Centis 2013[178]	Systematic review: methods are not adequate/unclear
Clark 2006[213]	Systematic review: methods are not adequate/unclear
Cruz 2012[227]	Conference abstract
Devore 2013[254]	Incorrect study design
Eslamparast 2014[282]	Incorrect interventions
Hayward 2010[412]	Conference abstract
Johnson 2010[474]	Systematic review: methods are not adequate/unclear
Jun 2013[481]	Conference abstract. Incorrect study design
Koot 2011[532]	Not review population
Kugelmas 2003[545]	Incorrect interventions
Larson-Meyer 2008[554]	Systematic review is not relevant to review question or unclear PICO
Liu 2014[592]	Study protocol
Madan 2005[614]	Incorrect interventions. Incorrect study design
Martin 2013[635]	Conference abstract
Monteiro 2012[665]	Conference abstract
Montesi 2013[666]	Conference abstracts
Moscatiello 2011[673]	Systematic review is not relevant to review question or unclear PICO. Systematic review: methods are not adequate/unclear
Moscatiello 2011[672]	Incorrect interventions
Nikroo 2015[697]	Not in English
Nobili 2006[700]	Incorrect interventions
Nobili 2006[705]	Incorrect study design
Nobili 2008[704]	Incorrect interventions
Oza 2009[726]	Incorrect study design
Park 1995[743]	Incorrect study design
Peng 2011[755]	Systematic review: methods are not adequate/unclear
Rafiq 2008[798]	Narrative review
Scaglioni 2013[845]	Incorrect study design
Shah 2009[862]	Not review population
Sreenivasa Baba 2006[911]	Incorrect study design
St George 2009[913]	Incorrect interventions
St George 2009[912]	Not review population. Includes Hep C population
Straznicky 2012[920]	Not review population
Thoma 2012[960]	Systematic review: methods are not adequate/unclear
Thoma 2012[957]	Conference abstract
Tilg 2010[962]	Systematic review is not relevant to review question or unclear PICO. Systematic review: methods are not adequate/unclear
Tock 2006[964]	Incorrect study design. Not review population
Vilar 2008[1002]	Incorrect interventions
Vilar Gomez 2009[1001]	Incorrect interventions
Vilar Gomez 2015 [1003]	Incorrect study design: no comparison
Wang 2003[1020]	Systematic review: methods are not adequate/unclear
Wang 2008[1017]	Less than minimum duration
Xiao 2013[1049]	Systematic review: methods are not adequate/unclear
Zelber-Sagi 2011[1087]	Systematic review is not relevant to review question or unclear PICO

M.10 Alcohol advice

Table 54: Studies excluded from the clinical review of alcohol advice

Reference	Reason for exclusion
Baker 2010[102]	Incorrect study design: cross sectional study design
Dunn 2012 [264]	Incorrect study design: cross sectional study design
Gunji 2009[370]	Incorrect study design: cross sectional study design
Gunji 2011[371]	Incorrect study design: cross sectional study design
Gunji 2012[372]	Incorrect study design: cross sectional study design
Hayashi 2004 [411]	Incorrect study design: cross sectional study design
Hiramine 2011 [422]	Incorrect study design: cross sectional study design
Kwon 2014 [549]	Incorrect study design: cross sectional study design
Lucey 2008 [602]	Incorrect study design: cross sectional study design
Moriya 2011[670]	Incorrect study design: cross sectional study design
Moriya 2013 [668]	Incorrect study design: cross sectional study design
Moriya 2015 [669]	Indirect population: included all causes of liver disease
Sinn 2014 [885]	Incorrect study design: cross sectional study design
Zatu 2015 [1079]	Incorrect study design: cross sectional study design

M.11 Fructose advice

Table 55: Studies excluded from the clinical review of fructose advice

Reference	Reason for exclusion
Abdelmalek 2010 [4]	Cross-sectional design only
Abid 2009[9]	Univariate analysis only
Anderson 2015[60]	No follow-up monitoring of NAFLD.
Assy 2008[84]	Univariate analysis only, and an indirect prognostic factor (soft drinks rather than fructose)
Cortez-Pinto 1999[224]	No relevant outcomes/ indirect study aim
Jin 2014 [472]	Univariate analysis only
Mager 2015 [617]	No relevant outcomes/ indirect study aim
O'Sullivan 2014[710]	Cross-sectional design only
Yilmaz 2012 [1062]	Narrative review
Volynets 2012 [1007]	Cross-sectional design only
Volynets 2013 [1008]	Univariate analysis only

M.12 Caffeine advice

Table 56: Studies excluded from the clinical review of caffeine advice

Study	Exclusion reason
Anty 2012[69]	Incorrect study design
Bambha 2014[109]	Incorrect study design
Birerdinc 2012[130]	Incorrect interventions
Gutierrez-Grobe 2012[376]	Incorrect study design

Molloy 2012[663]	Incorrect study design
Saab 2014[820]	Systematic review: quality assessment is inadequate
Yesil 2013[1061]	Systematic review: quality assessment is inadequate

M.13 Pharmacological interventions

Table 57: Studies excluded from the clinical review of pharmacological interventions

Study	Exclusion reason
Abdul 2009[5]	Conference abstract
Abenavoli 2010[7]	Incorrect interventions
Adams 2010[17]	No comparison
Hashemikani 2013[402]	Incorrect interventions
Alkhouri 2012[42]	Comment only
Amin 2009[58]	Patients liver function measures seem unrepresentative of UK NAFLD population and no explanation of units used to assess relevance.
Andreone 2011[62]	Conference abstract not available
Angelico 2007[63]	Systematic review: methods are not adequate/unclear
Anon 2014[2]	Incorrect interventions
Liu 2014[593]	Review article only
Dekeyser 2014[239]	Incorrect study design
Tzimalos 2014[982]	Review article only
Anon 2014[2]	Not in English
Musso 2013[675]	Not available
Arendt 2011[74]	Incorrect interventions
Argo 2009[77]	Incorrect study design
Armstrong 2010[80]	Conference abstract not available
Armstrong 2013[79]	Research protocol only
Athyros 2006[90]	Incorrect interventions
Athyros 2010[91]	Not review population. Incorrect interventions
Athyros 2011[87]	Incorrect interventions
Athyros 2013[88]	Not review population
Aubuchon 2011[92]	Incorrect interventions
Samson 2013[825]	Narrative review only
Balas 2007[104]	Not protocol outcome
Balmer 2008[106]	Conference abstract not available
Basu 2009[114]	Conference abstract
Botella-carretero 2010[138]	No comparison

Buranawuti 2007[154]	Conference abstract not available
Angelico 2007[63]	Systematic review is not relevant to review question or unclear PICO
Chalasani 2009[180]	Research protocol only
Chavez-tapia 2006[191]	Systematic review: study designs inappropriate
Cheng 2012[199]	Incorrect interventions
Vos 2012[1010]	Incorrect interventions
Copaci 2009[220]	Conference abstract
Corey 2014[223]	No relevant outcomes
Troisi 2013[974]	Not in English
Tock 2010[963]	Incorrect interventions
Del ben 2014[249]	No comparison
Della 2014[250]	Review article only
Akyuz 2007[27]	Incorrect interventions
Demiraj 2012[252]	Incorrect interventions
Nair 2004[683]	No comparison
Dufour 2005[262]	Conference abstract
Dufour 2010[261]	Comment only
Duseja 2007[265]	Incorrect interventions
Ebrahimi-mameghani 2014[268]	Incorrect interventions
Ersöz 2005[280]	Incorrect interventions
Eslami 2013[281]	Systematic review is not relevant to review question or unclear PICO
Federico 2006[296]	Incorrect interventions
Abel 2009[6]	Incorrect interventions. Inappropriate comparison
Foster 2011[315]	Incorrect interventions
Ekstedt 2007[274]	Incorrect interventions. Inappropriate comparison
Freemark 2007[326]	Not review population. Not guideline condition
Garinis 2010[339]	Incorrect interventions
Gastaldelli 2009[342]	Sufficient RCT evidence
Gastaldelli 2009[340]	Conference abstract
Gastaldelli 2010[341]	Outcome and analysis do not match protocol
Georgescu 2008[343]	Conference abstract
Georgescu 2009[344]	Inappropriate comparison
Gianturco 2013[351]	Incorrect interventions
Gomez 2006[359]	No comparison
Hussein 2007[443]	No comparison
Marconi 2011[632]	Inappropriate comparison

Pietu 2012[766]	Inappropriate comparison
Kiyici 2003[523]	Not review population
Hajiaghamohammadi 2012[379]	Less than minimum duration
Han 2014[391]	Incorrect interventions
Harrison 2003[399]	Incorrect interventions
Harrison 2004[396]	No comparison
Harte 2010[400]	Incorrect interventions
Haukeland 2008[410]	Conference abstract
Henriksen 2008[417]	Incorrect interventions
Hirata 2013[423]	Inappropriate comparison
Hoofnagle 2013[429]	Incorrect interventions
Hyogo 2008[445]	No comparison
Kimura 2010[518]	No comparison
Nakahara 2012[684]	Inappropriate comparison
Idilman 2008[448]	Incorrect interventions
Ohk 2012[713]	Cohort study
Kadayifci 2003[487]	Narrative only
Kargiotis 2014[495]	No comparison
Cankurtaran 2006[168]	Incorrect interventions
Kawamura 2013[499]	Incorrect study design
King 2007[520]	Comment only
Krakoff 2010[540]	Not review population
Lavine 2010[560]	Research protocol only
Lavine 2010[559]	Conference abstract not available
Lee 2006[573]	Conference abstract not available
Laurin 1996[558]	Incorrect interventions
Lindor 2004[588]	Narrative review
Lingvay 2012[589]	Incorrect interventions. Inappropriate comparison
Loguercio 2012[596]	Incorrect interventions
Promrat 2004[785]	No comparison
Loomba 2009[598]	Incorrect interventions
Macauley 2015[610]	Incorrect population
Madan 2005[614]	Incorrect interventions
Iqbal 2008[455]	Incorrect interventions. Inappropriate comparison
Marschall 2011[633]	Narrative review
Carulli 2013[172]	Not available

Mauras 2012[642]	Inappropriate comparison
McCormick 2015[646]	Incorrect intervention
Méndez-sánchez 2004[654]	Less than minimum duration
Morita 2005[667]	Incorrect interventions
Nar 2009[686]	Incorrect interventions
Milhaila 2009[657]	Incorrect interventions
Harrison 2004[397]	Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Nobili 2008[702]	Incorrect interventions
Ohki 2012[713]	Length of follow-up not clear
Omer 2010[714]	Incorrect interventions
Oni 2014[717]	Not review population
Orlic 2015[721]	Incorrect population
Patel 2010[751]	Incorrect interventions
Polyzos 2011[772]	Incorrect interventions
Preiss 2008[784]	Not review population
Ratziu 2009[805]	Conference abstract
Samy 2011[826]	Incorrect interventions
Sanyal 2002[834]	Conference abstract not available
Sanyal 2009[836]	Conference abstract not available
Sato 2015[843]	Systematic review, all studies included have already been reviewed for this report
Hatzitolios 2004[407]	Not review population
Serfaty 2007[857]	Narrative review
Shadid 2003[860]	No comparison
Shavakhi 2013[866]	Incorrect interventions
Shyangdan 2011[875]	Systematic review is not relevant to review question or unclear PICO
Sofer 2011[893]	Population taking other intervention medications not analysed separately. No relevant outcomes: primary outcomes vascular stiffness measurements (AI and PWV)
Sturm 2009[921]	Incorrect interventions
Riley 2008[812]	Inappropriate comparison
Sumida 2013[927]	Inappropriate comparison
Tiikkainen 2004[961]	Not review population
Tolman 2009[965]	Not review population
Iwasaki 2012[458]	Not review population

Torres 2009[971]	Conference abstract
Torres 2011[970]	Incorrect interventions
Torres 2011[969]	Conference abstract not available
Vacante 2011[987]	Incorrect interventions
Voican 2011[1006]	Narrative review
Wong 2012[1032]	health economic analysis
Wu 2012[1047]	Systematic review: quality assessment is inadequate
Yaginuma 2009[1053]	Conference abstract
Akiyama 2001[401]	No comparison
Ozelcoskun 2015[727]	Incorrect study design
Adams 2004[16]	No comparison
Zein 2012[1080]	Not protocol outcome
Zelber-sagi 2004[1083]	Conference abstract
Zeng 2014[1089]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate
Zhang 2014[1090]	Not review population
Zib 2007[1096]	Incorrect interventions

1

Appendix N: Cost-effectiveness analysis: diagnostic tests for NAFLD and advanced fibrosis

N.1 Introduction

For people with NAFLD, early and timely diagnoses of NAFLD (simple steatosis) and advanced liver fibrosis are necessary for the setup of a comprehensive care plan. This is highlighted by the fact that NAFLD is a reversible condition particularly in the early fibrosis stages. Failing to detect the disease at an early stage can have detrimental clinical effects for some high risk patients who are in danger of developing liver cirrhosis related complications such as jaundice, ascites, variceal bleeding, hepatic encephalopathy and hepatocellular carcinoma.

Amongst clinicians with an interest in the field, the only commonly agreed reference standard for the diagnosis of NAFLD and fibrosis is liver biopsy. By nature liver biopsy is an invasive test associated with adverse clinical events and disutility for some people. In addition, it is a resource intensive procedure, conducted with the guidance of ultrasound, which usually requires a day-case admission and has a considerable cost.

With the rising popularity of blood biomarkers associated with liver function and the increasing use of imaging tests that can diagnose and even stage NAFLD and fibrosis, without carrying the disadvantages of biopsy, these non-invasive liver tests (NILTs) have found their way into current clinical practice. However, the availability of the tests and way that these are embedded into clinical practice varies substantially across NHS providers. For these reasons the GDG prioritised original economic analysis to be conducted for the review questions that address objective diagnostic tests for the diagnoses of NAFLD and advanced fibrosis and who should be offered such testing.

The economic review did not identify any studies on diagnosing NAFLD and identified 2 studies (Steadman 2013 and Crossan 2015) that compared the cost-effectiveness of different fibrosis tests for NAFLD patients. Steadman conducted a cost-per-correct diagnosis analysis that compared transient elastography with liver biopsy and Crossan conducted a cost-per-correct diagnosis analysis that compared a variety of imaging modalities and serum markers with liver biopsy.

N.2 Methods

N.2.1 Model overview

N.2.1.1 Comparators

The model compares 7 non-invasive NAFLD tests and 12 non-invasive advanced fibrosis tests identified in the relevant clinical reviews. These are summarised below. Liver biopsy was also included in the analysis as the reference standard test carrying perfect sensitivity and specificity

For each diagnosis test comparison two additional strategies were also considered which did not include any tests:

- No test, treat all patients in the relevant population assuming they have advanced fibrosis
- No test, treat no-one, assuming none have advanced fibrosis until later clinical presentation

Table 58: Tests included in the model by disease aetiology

NAFLD (steatosis 5%)	Advanced fibrosis
CAP at 200-249	APRI at 0.98–1
Fatty liver index at 60	ARFI at 4.24
MRI PDFF at 6.87	AST/ALT at 0.8
MRS at 0-5	BARD at 2
Liver fat score at 0.16	ELF at 10.51
Steatotest at 0.38	Ferritin at 2x
Ultrasound	FIB4 at 1.45
	FibroTest at 0.47
	MRE at 4.15
	NAFLD fibrosis score at 0.676
	TE (M probe) at 7.8–7.9
	TE (XL) at 5.7

***AST**: aspartate transaminase enzymes; **ALT**: alanine transaminase enzymes; **CAP**: controlled attenuation parameter, **Fatty liver index**; BMI, waist circumference, triglycerides and GGT; **MRI**: Magnetic resonance imaging, **MRS;** magnetic resonance spectroscopy, Liver fat score: AST/ALT ratio, type 2 diabetes, fasting AST level, fasting insulin level, and MetS: **Steatotest**: Alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, alanine transaminase ,BMI, serum cholesterol, triglycerides, and glucose adjusted for age and gender; **APRI**: AST, ALT, platelet count; **BARD**: AST, ALT, BMI, type 2 diabetes, fasting glucose, **ELF**: enhanced liver fibrosis test including a serum concentration of procollagen-III aminoterminal-propeptide, tissue inhibitor of matrix metalloproteinase-1 and hyaluronic acid; **FIB4**: age, AST, ALT, platelets count; FibroTest: Alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, alanine transaminase; MRE: magnetic resonance elastography; **NAFLD fibrosis score**: Age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio; **TE**: Transient elastography*

N.2.1.1.1 Combinations of more than 1 test

In planning the model structure, the GDG considered strategies using 2 of the single tests (excluding liver biopsy) consecutively. The GDG considered that combinations should include 1 blood test and 1 imaging test as these would be likely to give independent results. The most promising combination would be one using a blood test with high sensitivity (to maximise true positives and minimise false negatives) followed by an imaging test with high specificity (to rule out true negatives). However, when viewing the diagnostic accuracy values found in the clinical review (see Section **Error! eference source not found.** below) no such combination could be found. Consequently there was no reason to believe any combination of 2 tests would give more accurate results than the best single tests, but with an increased cost for using 2 tests instead of 1. Therefore no such combinations were modelled.

N.2.1.2 Population

For NAFLD testing, the examined population was people suspected of having NAFLD with an age of 45 years. The age was obtained from studies included in the relevant review. For advanced fibrosis testing, the population was NAFLD patients suspected of having advanced fibrosis with an age of 50 years. The age was set at this level to simulate the progression of the disease and took into account the age at diagnosis of advanced liver disease.

N.2.1.3 Time horizon, perspective, discount rates used

The analysis will follow the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and the perspective of the UK NHS and personal social services. A lifetime horizon has been chosen to fully capture the adverse outcomes derived from incorrect diagnosis.

N.2.2 Approach to modelling

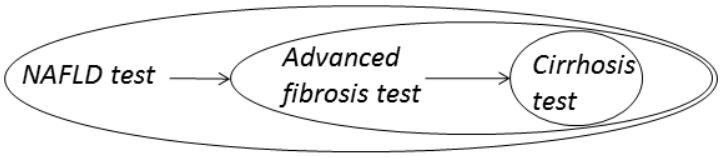
The model structure attempts to simulate the whole NAFLD disease pathway from NAFLD diagnosis to liver transplant. Since the clinical review did not identify any reliable non-invasive diagnostic tests for the identification of NASH or any level of fibrosis, NAFLD progression in the model is broken down in the following health states:

- NAFLD without advanced fibrosis (<F3)
- NAFLD with advanced fibrosis (F3)
- NAFLD cirrhosis (F4)

Although the clinical definition of advanced fibrosis usually includes both F3 and F4 fibrosis levels, these are separated here for modelling purposes.

To estimate the cost-effectiveness of tests to diagnose NAFLD (steatosis 5%), advanced fibrosis and cirrhosis, the pathway was broken down into 3 sections. The NAFLD test section, the advanced fibrosis test section and the cirrhosis test section. The cirrhosis test section is thoroughly discussed as part of the cirrhosis guideline. Model sections were constructed as standalone models and each one runs in relation to the next as exhibited in **Error! Reference source not found.** below.

Figure 382: Nested model sections



Each section follows a similar structure incorporating two phases:

- **Decision tree:** Using the sensitivity and specificity, combined with data on the prevalence of the condition (NAFLD, advanced fibrosis, cirrhosis) in each of the target populations, the models identify the proportion of people who receive a true positive (TP), true negative (TN), false positive (FP) or false negative (FN) diagnosis.
- **Markov model:** Once the diagnosis is made people move into the second part of the models which involve a Markov model to fully evaluate long-term health and cost outcomes for people starting with each diagnosis. The model has 6-monthly cycles and continues until death or age 100 years.

Further information and technical details are provided below.

N.2.2.1 NAFLD section

N.2.2.1.1 Model structure

Figure 383: Graphical depiction of the decision tree

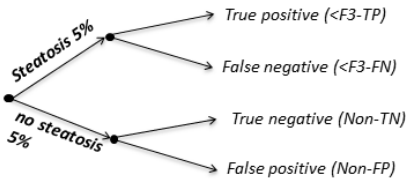
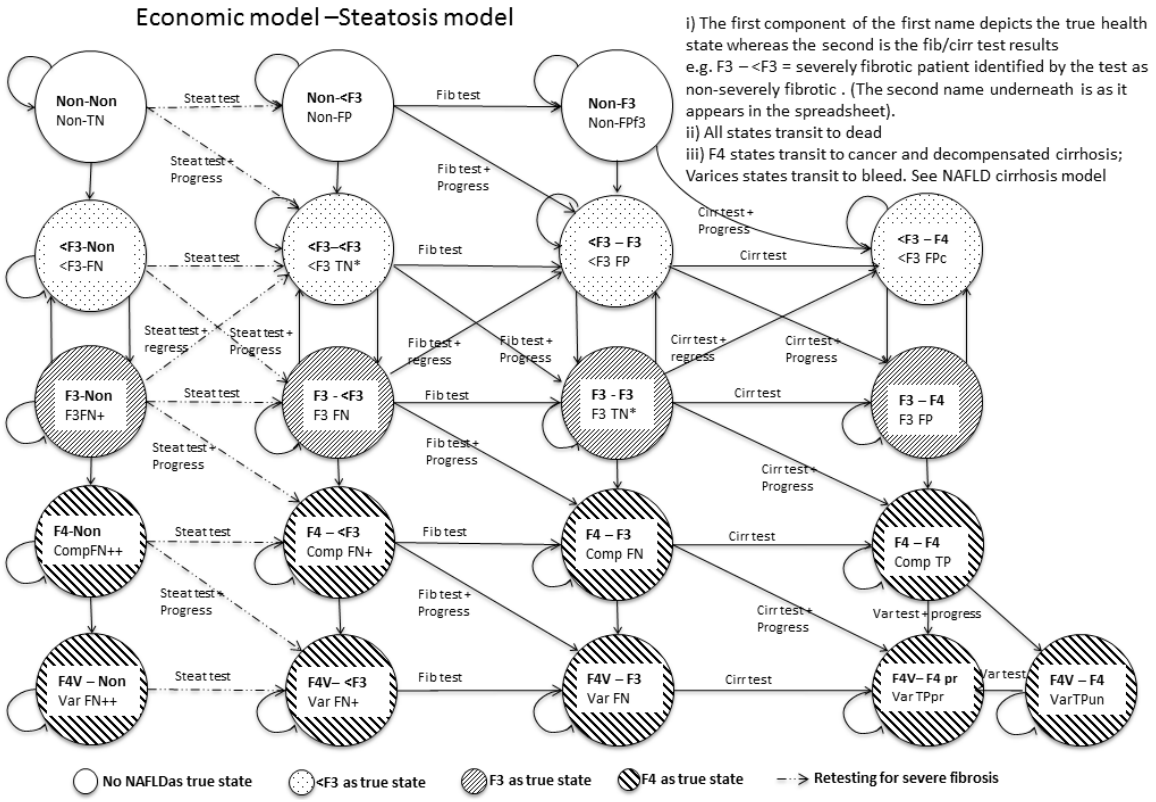


Figure 384: Graphical depiction of the Markov model



Initially, a decision tree determines the proportion of people with NAFLD who receive a correct diagnosis (true positive - TP) and an incorrect diagnosis (false negative - FN); and the proportion of people without NAFLD who receive a correct diagnosis (true negative – TN) and an incorrect diagnosis (false positive – FP) depending on the diagnostic accuracy of every test. If identified having NAFLD, patients undergo fibrosis testing.

Consequently, patients enter the Markov model through 10 health states as presented in **Error! eference source not found.** and **Error! Reference source not found.**:

- Non-Non
- <F3-Non
- Non-<F3
- <F3-<F3
- F3-Non
- F4-Non
- F4V-Non
- F3-<F3
- F4-<F3
- F4V-<F3

A positive steatosis 5% test result is accompanied by a short term lifestyle modification intervention and by monitoring those people for the development of advanced fibrosis. Individuals with a negative test result progress or regress asymptomatically and are only identified either upon presentation with a decompensation event or after a NAFLD retest. The model also includes two health states where people have consecutive wrong diagnoses of NAFLD, advanced fibrosis and cirrhosis (Non-F3, <F3-F4). As a simplification, the model does not include the extreme scenario where a patient could have 3 consecutive misdiagnoses (an individual without NAFLD diagnosed with cirrhosis).

Who to test for NAFLD

To determine the level of cost-effectiveness of NAFLD testing across subgroups with a specific risk factor (e.g. BMI>30, type 2 type 2 diabetes, metabolic syndrome) the prevalence of NAFLD for each subgroup was used sequentially in the model.

Optimal testing frequency (for those with a negative result)

To determine the optimal testing frequency for those with a negative diagnosis result, the model was run multiple times for different combinations of risk factors and testing frequencies.

N.2.2.2 Advanced fibrosis section

N.2.2.2.1 Model structure

Figure 385: Graphical depiction of the decision tree

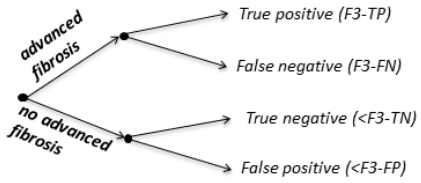
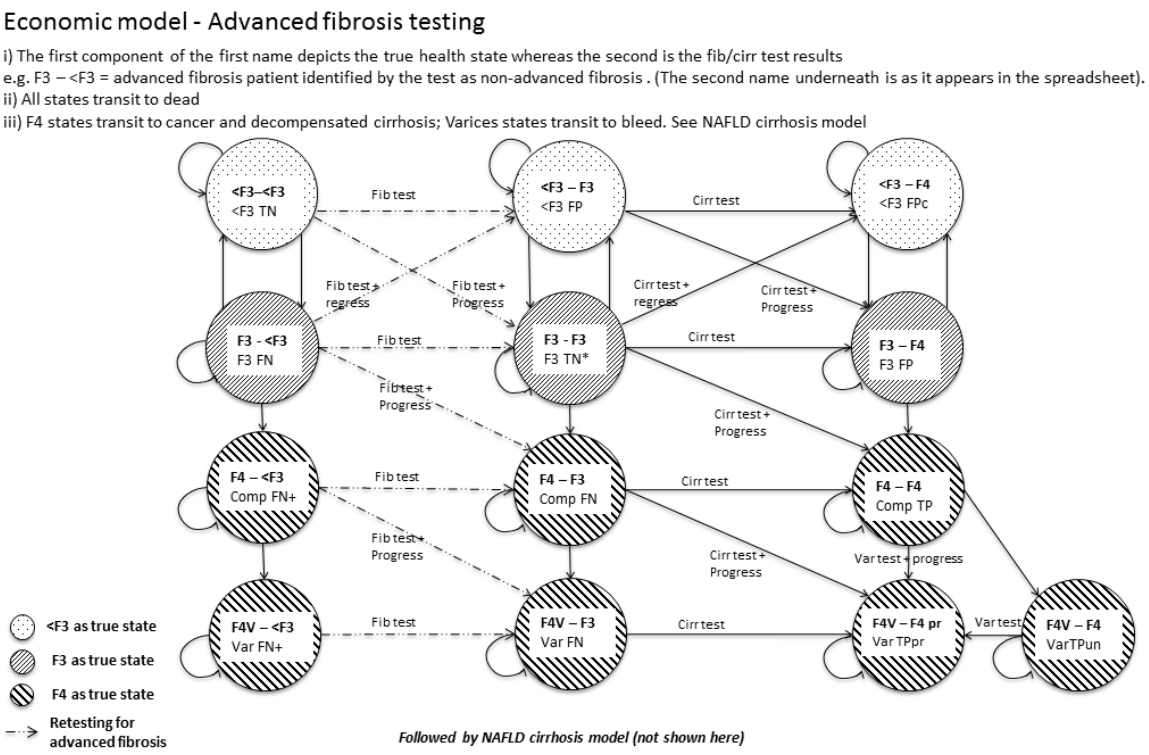


Figure 386: Graphical depiction of the Markov model



Initially, a decision tree determines the proportion of people with advanced fibrosis who receive a correct diagnosis (true positive - TP) and an incorrect diagnosis (false negative - FN); and the proportion of people without advanced fibrosis who receive a correct diagnosis (true negative – TN) and an incorrect diagnosis (false positive – FP) depending on the diagnostic accuracy of every test. If identified having advanced fibrosis patients undergo cirrhosis testing.

Consequently, patients enter the Markov model through 12 health states as presented in **Error! Reference source not found.**Figure 386 and Figure 388:

- <F3-<F3
- F3-<F3
- <F3-F3
- F3-F3<F3-F4
- F4-<F3
- F4V-<F3
- F3-F4
- F4-F4
- F4-F3
- F4V-F4pr
- F4V-F3

A positive advanced fibrosis test result is accompanied by a treatment with either pioglitazone or vitamin E and by monitoring those people for the development of cirrhosis. Individuals with a negative test result progress or regress asymptomatically and are only identified either upon presentation with a decompensation event or after retesting for advanced fibrosis. The model also

includes a health state where people have consecutive wrong diagnoses of advanced fibrosis and cirrhosis (<F3-F4).

Who to test for advanced fibrosis

To determine the level of cost-effectiveness of advanced fibrosis testing across subgroups with a specific risk factor (e.g. hypertension) the prevalence of advanced fibrosis for each subgroup was used sequentially in the model.

Optimal testing frequency (for those with a negative result)

To determine the optimal testing frequency for those with a negative diagnosis result, the model was run multiple times for different combinations of risk factors and testing frequencies.

N.2.2.3 Cirrhosis section

N.2.2.3.1 Model structure

Figure 387: Graphical depiction of the decision tree

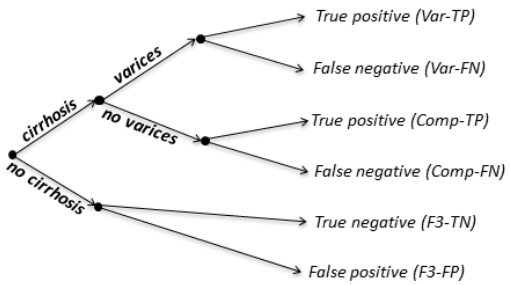
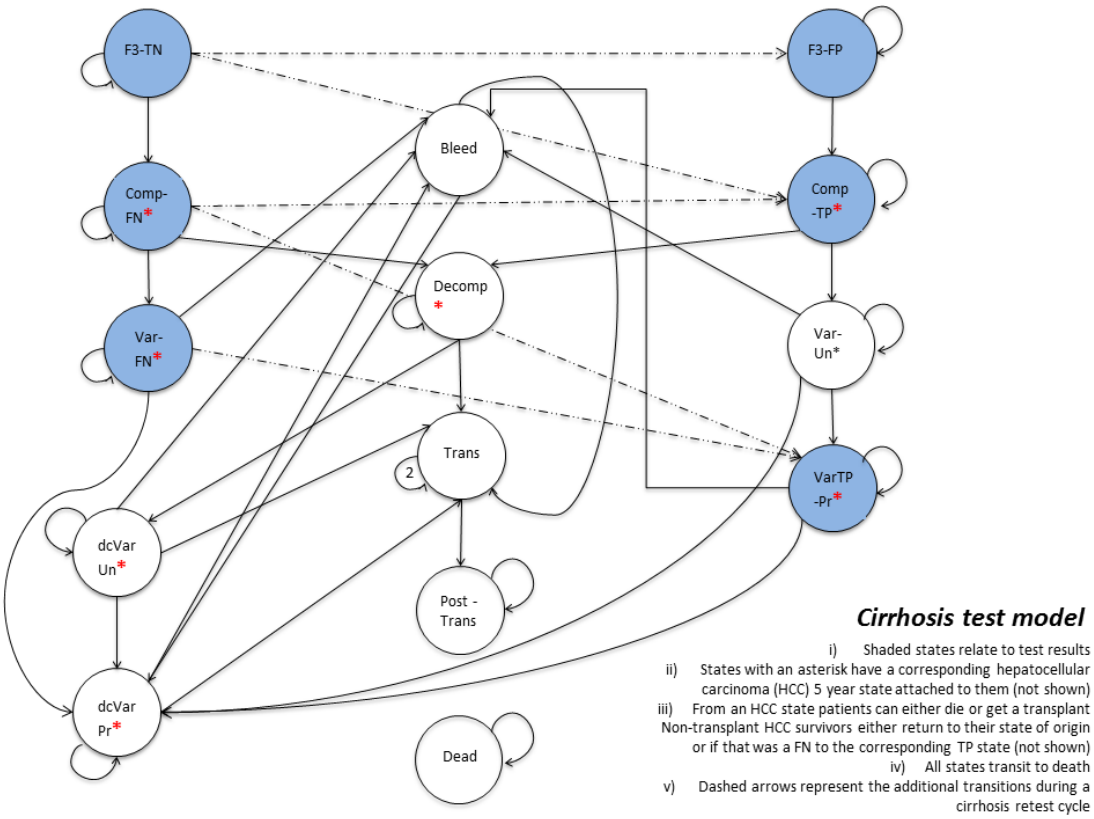


Figure 388: Graphical depiction of the Markov model



The cirrhosis model structure is thoroughly discussed in the relevant appendix of the NICE cirrhosis guideline.

N.2.2.4 Benefits of diagnosis

N.2.2.4.1 Early NAFLD model section

People diagnosed with NAFLD receive a lifestyle modification intervention. Intervention cost and effectiveness data were sourced from a relevant economic model that was part of recent NICE public health guidance (PH53). Per patient costs were estimated through a systematic literature review. Intervention effectiveness was expressed in quality of life gain as a result of post intervention BMI loss. The PH53 analysis also took into account an annual weight regain which reduced the QoL gain through time. For the present model, QoL gain was adjusted according to the average BMI, age and sex characteristics of the studies included in the diagnostic review. Due to the annual weight regain, this QoL gain was expressed as a temporary QoL increase of 18 months (3 model cycles).

N.2.2.4.2 Advanced fibrosis model section

People with NAFLD diagnosed with advanced fibrosis will receive a treatment with either pioglitazone or vitamin E (depending on patient profile). Drug effectiveness data were sourced from Sanyal 2010 who conducted a randomised controlled trial on 247 patients with non-alcoholic steatohepatitis. Unit costs for pioglitazone and vitamin E were sourced from BNF and an NHS hospital trust (GDG source) respectively.

N.2.2.4.3 Cirrhosis model section

This section is discussed in the relevant appendix of the cirrhosis guideline.

N.2.2.5 Uncertainty

N.2.2.5.1 Probabilistic sensitivity analysis

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 12,000 times for the steatosis model and 5,000 times for the fibrosis model – and results were summarised.

The way in which distributions are defined reflects the nature of the data, so for example proportions were given a beta distribution, which is bounded by 0 and 1, reflecting that they cannot be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 59 and in the relevant input summary tables in Section N.2.3. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 59: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Specificity[(a)] Transition probabilities	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and Beta values were calculated as follows: Alpha=(True negatives) Beta=(Number of patients)-(True negatives)
Diagnostic odds ratio[(a)]	Lognormal	Derived from the ln(DOR) and Se(ln(DOR))
Utilities	Lognormal applied on utility decrements	Mean = ln(mean cost) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2
Costs (tests, treatments)	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. SE was set at deterministic cost/4. Alpha and Beta values were calculated as follows: Alpha = $(mean/SE)^2$ Beta = SE^2/Mean
Relative risk ratio	Lognormal	Mean = ln(mean cost) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2

(a) The sensitivity is calculated from the specificity and the diagnostic odds ratio

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- prevalence of NAFLD in each population
- drug costs
- RR applied on the bleeding probability as a benefit of monitoring for varices.

The RR was sourced from a review (Berzigotti 2013) that did not report any accompanying measures of uncertainty around the point estimate. Drug costs used the (current) set price for the NHS. Prevalence varied between risk group cohorts investigated, and so testing the different cohorts demonstrated the effect of varying prevalence.

N.2.2.5.2 Deterministic sensitivity analysis

In addition, various one way and multiway deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, 1 or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

Apart from assigning distributions to most of the model parameters, deterministic sensitivity analysis was also performed for a variety of variables.

Table 60: Parameters tested in DSA

Parameter	Change
NAFLD model (one-way DSA)	
GP appointments for testing strategies	+1 for each test
Other-cause mortality	+50%, +100%
Liver-related mortality	-25%, -50%
Transition probability - No NAFLD → NAFLD (F012)	-25%, -50%
Transition probability – NAFLD (F012) → F3	-25%, -50%
Transition probability – F3 → CompCirr	-25%, -50%
Transition probability – CompCirr → decomp	-25%, -50%
Lifestyle modification intervention	Removed, +100% effectiveness
FLI unit cost	-25%, +25%
Ultrasound unit cost	-25%, +25%
Discount rate	1.5%
FLI diagnostic accuracy	Low CI for sens, low CI for spec, low CI for sens and spec
Fibrosis test	ARFI instead of ELF
NAFLD model (multiway DSA)	
Scenario 1	Liver-related mortality: -50% / other-cause mortality: +50% / TP No NAFLD→ F012, F012→F3, F3→F4: -20%
Scenario 2	Starting age 58 / +1 GP appointments per test
Scenario 3	Starting age 58 / +1 GP appointments per test / without lifestyle modification intervention
Advanced fibrosis model	
ELF unit cost	-25%, +25%
Other-cause mortality	+50%, +100%
Liver-related mortality	-25%, -50%
Transition probability – NAFLD (F012) → F3	-25%, -50%
Transition probability – F3 → CompCirr	-25%, -50%
Drug treatment	Removed, -33% effectiveness, +33% effectiveness
Discount rate	1.5%
ELF diagnostic accuracy	Low CI for sens, low CI for spec, low CI for sens and spec
Cirrhosis test	ARFI instead of TE

N.2.3 Model inputs

N.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated by clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in

Table **61** below. More details about sources, calculations and rationales for selection can be found in the sections following this summary table.

Table 61: Summary of base-case model inputs

Input	Value
Patient age at NAFLD diagnosis	45 years
Patient age at advanced fibrosis	50 years
Patient age at cirrhosis diagnosis	50 years
Time horizon	Lifetime
Discount rate	Costs = 3.5%; effects = 3.5%

Table 62: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimates		Probability distribution	Distribution parameters
Prevalences				
NAFLD				
Obese (BMI≥30)	46%		n/a – point estimate tested on DSA	
Wide waist circumference (≥102cm for men, ≥88cm for women)	36%		n/a – point estimate tested on DSA	
Type 2 diabetes (Glyceamia≥110mg/dl)	53%		n/a – point estimate tested on DSA	
Low HDL (<40mg/dl men, <50mg/dl women)	36%		n/a – point estimate tested on DSA	
High triglycerides (≥150mg/dl)	46%		n/a – point estimate tested on DSA	
Metabolic syndrome (NCEP criteria)	54%		n/a – point estimate tested on DSA	
Advanced fibrosis				
Baseline	15%		n/a – point estimate tested on DSA	
Hypertension	34%		n/a – point estimate tested on DSA	
Type 2 diabetes	29%		n/a – point estimate tested on DSA	
Metabolic syndrome	33%		n/a – point estimate tested on DSA	
Obese (BMI≥30)	22%		n/a – point estimate tested on DSA	
Diagnostic accuracy (NAFLD)	Sensitivity	Specificity		Diagnostic odds ratio
CAP	0.91	0.52	Lognormal	10.91
Fatty liver index	0.76	0.87	Lognormal	20.64
MRI	0.87	0.98	Sampled from the joint posterior distribution (WinBUGS iterations)	

Parameter description	Point estimates		Probability distribution	Distribution parameters
MRS	0.87	0.82	Sampled from the joint posterior distribution (WinBUGS iterations)	
Ultrasound	0.64	0.87	Sampled from the joint posterior distribution (WinBUGS iterations)	
LFS	0.65	0.87	Lognormal	12.10
Steatotest	0.87	0.50	Lognormal	6.64
Diagnostic accuracy (Advanced fibrosis)	Sensitivity	Specificity		Diagnostic odds ratio
APRI at 0.98–1	0.55	0.85	Sampled from the joint posterior distribution (WinBUGS iterations)	
ARFI at 4.24	0.9	0.89	Lognormal	76.50
AST/ALT at 0.8	0.68	0.62	Sampled from the joint posterior distribution (WinBUGS iterations)	
BARD at 2	0.79	0.61	Sampled from the joint posterior distribution (WinBUGS iterations)	
ELF at 10.51	0.94	0.98	Lognormal	697
Ferritin at 2x	0.16	0.92	Lognormal	2.19
FIB4 at 1.45	0.91	0.64	Lognormal	17.23
FibroTest at 0.47	0.60	0.90	Lognormal	13.63
MRE at 4.15	0.85	0.93	Lognormal	70.84
NFS at 0.676	0.41	0.95	Sampled from the joint posterior distribution (WinBUGS iterations)	
TE (M) at 7.8–7.9	0.91	0.72	Sampled from the joint posterior distribution (WinBUGS iterations)	
TE (XL) at a 5.7	0.91	0.54	Lognormal	11.43
Utilities (NAFLD)				
NAFL-NASH (F012)	0.84		Lognormal on decrement	SE=utility decrement/4
NAFL-NASH (F012)- treated	0.87		Lognormal on decrement	SE=utility decrement/4
Fibrosis F3	0.72		Lognormal on decrement	SE=utility decrement/4
Compensated cirrhosis	0.60		Lognormal on decrement	SE=utility decrement/4
Decompensated cirrhosis	0.54		Lognormal on decrement	SE=utility decrement/4
Varices	0.60		Lognormal on decrement	SE=utility decrement/4
Variceal bleeding	0.54		Lognormal on decrement	SE=utility decrement/4
Hepatocellular carcinoma	0.54		Lognormal on decrement	SE=utility decrement/4
Liver transplant	0.80		Lognormal on decrement	SE=utility decrement/4
Post liver transplant	0.85		Lognormal on decrement	SE=utility decrement/4
Test costs (£)				

Parameter description	Point estimates		Probability distribution	Distribution parameters
Fatty liver index	7.19		n/a -estimated as a combination of other tests	
Steatotest	44.83		Gamma	SE=mean/4
NAFLD liver fat score	19.41		n/a -estimated as a combination of other tests	
Ultrasound	49.00		Gamma	SE=mean/4
MRI	143.00		Gamma	SE=mean/4
MRS	143.00		Gamma	SE=mean/4
CAP	68.00		Gamma	SE=mean/4
Liver biopsy	639.61		Gamma	SE=mean/4
Transient elastography	68.00		Gamma	SE=mean/4
ARFI-VTq	50.96		n/a -estimated as a combination of other tests	
MRE	169.02		n/a -estimated as a combination of other tests	
ELF	111.06		Gamma	SE=mean/4
FibroTest (one threshold)	44.83		Gamma	SE=mean/4
Fib4 (one threshold)	4.52		Gamma	SE=mean/4
AST/ALT ratio	5.41		n/a -estimated as a combination of other tests	
APRI	4.16		Gamma	SE=mean/4
BARD	5.41		n/a -estimated as a combination of other tests	
Ferritin at 2x	4.00		Gamma	SE=mean/4
NFS	5.09		Gamma	SE=mean/4
Other test costs (£)				
Full blood count	2.71		Gamma	SE=mean/4
INR	2.94		Gamma	SE=mean/4
Urea-electrolytes	3.00		Gamma	SE=mean/4
LFT	4.48		Gamma	SE=mean/4
Monitoring test costs (£)				
Diagnostic Endoscopy	205.66		Gamma	SE=mean/4
Ultrasound	49.00		Gamma	SE=mean/4
AFP	1.42		Gamma	SE=mean/4
Staff costs (£)				
GP consultation	67.00		Gamma	SE=mean/4
GP practice nurse consultation	17.67		Gamma	SE=mean/4
Hepatologist - first appointment	217.00		Gamma	SE=mean/4
Hepatologist - follow up	176.00		Gamma	SE=mean/4
Hospital nurse	19.33		Gamma	SE=mean/4
Hospital dietitian	12.33		Gamma	SE=mean/4
Hospital pharmacist	32.00		Gamma	SE=mean/4
Procedure and Drug costs (£)				
Band Ligation	1325.83		Gamma	SE=mean/4

Parameter description	Point estimates		Probability distribution	Distribution parameters
Variceal bleeding treatment	2653.29		Gamma	SE=mean/4
***Decompensation costs* (6-monthly)**			Gamma	
Inpatient days	4568.89		Gamma	SE=mean/4
Procedures	1204.42		Gamma	SE=mean/4
Drugs	163.81		Gamma	SE=mean/4
NAFLD treatments				
Pioglitazone	9.42		n/a	
Vitamin E	51.24		n/a	
Lifestyle modification intervention	100.00		n/a	
Liver Transplant state costs (£) – 6-monthly				
NAFLD				
Liver transplant - Year 1	29,574.51		Gamma	SE=mean 4
Liver transplant - Year 2	9185.77		Gamma	SE=mean 4
Post liver transplant	4198.03		Gamma	SE=mean 4

Abbreviations: AFP: alpha-fetoprotein blood test; APRI: Aspartate aminotransferase to platelet ratio index; ARFI: Acoustic radiation force impulse imaging; AST/ALT: Aspartate aminotransferase to alanine aminotransferase; Castera algorithm: combination of transient elastography, FibroTest and liver biopsy; ELF: Enhanced liver fibrosis test; INR: International normalized ratio; LFT: liver function blood test; SAFE algorithm: combination of FibroTest, APRI and liver biopsy; TE: Transient elastography

N.2.3.2 Prevalence of NAFLD and advanced fibrosis

To compare the cost-effectiveness of testing patients with various risk factors, prevalence values of NAFLD were sourced from Caballeria 2010, a cross sectional study of 766 individuals examining the prevalence and factors associated with NAFLD. This paper was identified in the risk-factors literature review and it was the only study that reported tabulated results with cut-off values for the various risk factors (e.g. BMI≥30, glycaemia≥110mg/dl) which allowed their use in the economic model.

For advanced fibrosis, the base case prevalence was obtained from the Singh 2015 meta-analysis. This was estimated through the proportion of NAFLD patients with a fibrosis level >F2 at baseline. Prevalence figures for specific subgroups with every risk factor (type 2 diabetes, hypertension, metabolic syndrome, obesity) were obtained from McPherson 2014 and Marchesini 2003; sources provided by the GDG.

N.2.3.3 Diagnostic accuracy

N.2.3.3.1 NAFLD and advanced fibrosis models

The diagnostic review identified accuracy data for more than one threshold per test. For practical reasons the GDG selected one threshold per test for the model cost-effectiveness comparisons. Selection criteria included the current acceptability of the thresholds in clinical practice, the appropriateness of the diagnostic accuracy characteristics of every threshold (high sensitivity or specificity) and the quality of the evidence. In the case of MRI for diagnosing NAFLD, the literature review identified papers using 6 different techniques. Due to differences in the way MRI PDFF was performed in the various studies included in the review, its diagnostic accuracy was not pooled and therefore a single source was chosen. For ELF, to represent the uncertainty around its diagnostic accuracy and because the log-normal distribution could not fit onto a test with a 100% sensitivity, its 2×2 table was adjusted by adding 0.5 patients in each of the four diagnostic outcomes. This brought down its sensitivity from 100 to 94. Details on the selection criteria follow in Table 63.

Table 63: Threshold selection by test

Diagnostic test for	Test-threshold	Source	Reason
NAFLD	MRI PDFF at 6.87 threshold	Paparo 2015	Due to the combination of its relative technique simplicity and the use of a 1.5 Tesla scanner
Advanced fibrosis	APRI at 0.98–1	6 studies – meta-analysis	Greater confidence on this threshold as its diagnostic accuracy data came from 6 studies compared to only 1 for the other thresholds
Advanced fibrosis	ARFI at 4.24	Palmeri 2011	Larger patient cohort
Advanced fibrosis	AST/ALT at 0.8	8 studies – meta-analysis	Due to the higher acceptability of the threshold in current clinical practice
Advanced fibrosis	ELF at 10.51	Nobili 2009	The only study using the current ELF system, lower risk of bias
Advanced fibrosis	Ferritin at 2x	Angulo 2014	GDG choice based on high specificity that the threshold offers
Advanced fibrosis	FIB4 at 1.45	Sumida 2012	Due to the high sensitivity this threshold offers
Advanced fibrosis	FibroTest at 0.47	Adams 2011	Study conducted by an independent research team (the other source was from the team that developed the test)
Advanced fibrosis	MRE at 4.15	Kim 2013	Larger cohort of patients offering narrower confidence intervals
Advanced fibrosis	NFS at 0.676	12 studies – meta-analysis	Due to the high specificity that this threshold offers
Advanced fibrosis	TE (M) at 7.8–7.9	3 studies – meta-analysis	Due to the high sensitivity and the relatively moderate specificity
Advanced fibrosis	TE (XL) at 5.7	Wong 2012	Due to the high sensitivity and the relatively moderate specificity

To account for uncertainty around diagnostic accuracies and correlation between sensitivity and specificity a joint distribution was used when making diagnostic accuracies probabilistic. First of all the diagnostic odds ratio (DOR) was calculated for the diagnostic test:

$$DOR = \frac{sensitivity}{1 - sensitivity} * \frac{specificity}{1 - specificity}$$

The standard error of the log DOR was calculated using the absolute values for the number of TP, TN, FP and FN:

$$SE(\ln(DOR)) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$$

Using these equations a normal distribution was fitted around the log of the DOR.

Once the DOR is calculated the sensitivity can become a function of the DOR and the specificity:

$$sensitivity = 1 - \frac{specificity}{specificity + (1 - specificity) * DOR}$$

Finally a beta distribution was fitted around the specificity therefore when probabilistic sensitivity analysis is conducted the specificity will change in accordance to the overall diagnostic uncertainty and its relationship with the sensitivity.

When reviewers identified more than 2 studies for a specific test, pooled diagnostic accuracy figures were estimated with the use of Bayesian methods. To account for uncertainty around these figures random samples were drawn from the original joint posterior distribution (WinBUGS iterations) for the purposes of probabilistic sensitivity analysis.

N.2.3.4 Baseline transition probabilities

Relevant transition rates were sought in the literature and were confirmed by the GDG as appropriate for use in the current model. All transition rates were transformed to 6-monthly transition probabilities.

Table 64: NAFLD – 6-monthly transition probabilities

From	To	Value	Source
No NAFLD	NAFLD (F012)	0.020	Xu 2013, Hamabe 2011, Sung 2012, Kim 2014C, Lee 2010
Fibrosis F012	Fibrosis F3	0.027	Singh 2015
Fibrosis F3	Fibrosis F012	0.054	Singh 2015
Fibrosis F3	Compensated cirrhosis	0.028	Singh 2015
Compensated cirrhosis	Decompensated cirrhosis	0.035	Hui 2003
Compensated cirrhosis	Compensated cirrhosis with varices	0.030	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with varices	0.051	Berzigotti 2013
Compensated cirrhosis with varices	Bleeding	0.061	NIEC 1988
Decompensated cirrhosis with varices	Bleeding	0.133	NIEC 1988
Compensated/Decompensated cirrhosis	HCC	0.013	Ascha 2010
Decompensated cirrhosis/HCC/bleeding	Transplant	0.009	Average from HBV and HCV cohorts
Fibrosis F012	Death	0.027	Younossi 2011
Fibrosis F3	Death	0.003	Younossi 2011
Compensated cirrhosis	Death	0.011	Younossi 2011
Decompensated cirrhosis	Death	0.114	Average from HBV and HCV cohorts
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.337	Dakin 2010 (from HBV cohort)
Transplant	Death	0.095	Average from HBV and HCV cohorts
Post-transplant	Death	0.022	Average from HBV and HCV cohorts

An average NAFLD development rate was sourced from the studies identified in the risk factor literature review and was assumed to represent a mixed risk factor cohort. Transition probabilities for the progression/regression of people with NAFLD up to the point of cirrhosis were obtained from the Singh 2015 meta-analysis of studies with a paired biopsy study design. The decompensation rate was sourced from Hui 2003, a study observing the long-term outcomes of cirrhosis in people with non-alcoholic steatohepatitis (NASH). The figures on the prevalence of varices in people with cirrhosis were sourced from a review conducted by Berzigotti 2013; these were adjusted by assuming

that two-thirds of varices were medium to large. Bleeding rates were obtained from a prospective study of 321 patients with cirrhosis and varices and no history of bleeding conducted by the North Italian Endoscopic Club (NIEC 1988). Mortalities for the different fibrosis stages were sourced from Younossi et al 2011; who examined the liver related mortality of 257 patients with different levels of fibrosis. Bleeding mortality was sourced from Stevenson 2012, based on clinical judgement. The incidence of HCC was obtained from Ascha 2010, a study evaluating the incidence and risk factors of HCC in 195 NASH patients. It was assumed that this rate applied both to people with compensated cirrhosis and those with decompensated cirrhosis. Due to the lack of published evidence for the remaining transition probabilities, the GDG agreed that those from the hepatitis cohorts would be the most appropriate. These originated from the Wright 2006 UK HTA and an economic evaluation on HBV drugs conducted by Dakin et al 2010.

N.2.3.5 Life expectancy and mortality rates

Life tables for England and Wales, published by the Office of National Statistics (ONS) based on 2011–2013 mortality data were used to establish population mortality rates for men and women for ages 45 to 100 years.[712] ONS 2013 mortality statistics for England and Wales by cause of death[697,698] were used to calculate the proportion of deaths for each 5-year age group which were due to liver related or non-liver related causes. These proportions were applied to the mortality rates to give the risk of death due to non-liver related causes for each annual age group for both men and women.

N.2.3.6 Utilities

The systematic literature review identified a variety of evidence on NAFLD patients. In the majority of this evidence authors did not report QoL results per liver disease state (fibrosis, compensated cirrhosis, decompensated cirrhosis). In addition, a range of relevant literature could not be used due to the lack of available mapping algorithms for transformation to EQ-5D utilities. A study conducted by David et al. 2009 reported a QoL estimate specifically on non-NASH NAFLD patients (0.52) however this was considered too low by the NAFLD GDG and not appropriate to be used in the economic model.

As an alternative, the NAFLD GDG suggested using the utility attributed to patients with obesity as a baseline for QoL of non-NASH NAFLD patients. This value was obtained from recent NICE public health guidance (PH53) that simulated the relation of BMI with quality of life in two-dimensional tables. To acquire utilities for the remaining model health states we estimated them as the product of the baseline value by the proportional difference in utility of a similar set of utilities from a hepatitis B subgroup.

N.2.3.7 Resource use and cost

N.2.3.7.1 Diagnostic test costs

The majority of unit costs were sourced from two relevant published HTAs [226,257] and the NHS 2013-14 Reference cost schedule. The cost of ARFI VTq was built on top of the ultrasound NHS tariff (NHS reference costs 2013-14) assuming an extra kit has to be acquired for an ARFI examination. The cost of the kit was sourced from the relevant NICE M-Tec assessment.[688] A machine lifespan of 5 years with 500 Ultrasound/ARFI scans per year was assumed after GDG guidance. The cost of MRE was built on top of the MRI NHS tariff (NHS reference costs 2013-14) assuming an extra kit has to be acquired for an MRE examination. The cost of the kit was set at £80,000 and was provided by the GDG. A figure of 350 MRE scans per machine/per year for 10 years was also provided by the GDG.

Table 65: Test unit costs

Test	Cost	Source	Comment
Liver biopsy	639.61	NICE MTG027	
NAFLD			
Fatty liver index	7.19	Estimation	Based on the cost of individual parameters
Liver fat score	19.41	Estimation	Based on the cost of individual parameters
Steatotest	44.83	Assumption	Assumed equal to the cost of FibroTest
Ultrasound	49.00	NHS reference costs 2013/14	RA23Z, Ultrasound scan less than 20 minutes
CAP	68.00	NHS hospital trust	Provided by GDG member
MRI-MRS	143.00	NHS reference costs 2013/14	RA01A, Magnetic Resonance Imaging Scan, one area, no contrast, 19 years and over
Fibrosis			
APRI	4.16	Crossan 2015	
AST/ALT ratio	5.41	Crossan 2015-Donnan 2009	Assumed to equal the cost of an LFT plus the cost of an extra biomarker
BARD	5.41	Crossan 2015-Donnan 2009	Assumed similar to AST/ALT ratio
Ferritin	4.00	NHS hospital trust	Provided by GDG member
FIB4	4.52	Crossan 2015	
NFS	5.09	Crossan 2015	
ELF	111.06	Crossan 2015	
FibroTest	44.83	Crossan 2015	
TE	68.00	NHS hospital trust	Provided by GDG member
ARFI	50.96	Assumption	Built on top of ultrasound NHS tariff – see above
MRE	169.02	Assumption	Built on top of MRI NHS tariff – see above

(a) All values were inflated to 2013/14 prices

N.2.3.7.2 Drugs

Unit costs were sourced from BNF 69 for pioglitazone and an NHS hospital trust for vitamin E. The dosages were kept consistent to that of the evidence considered in the relevant clinical literature review.

Table 66: 6-monthly drug unit costs

Test	Cost	Source	Comment
Vitamin E	51.24	NHS hospital trust - GDG source	Assuming 30mg daily – £8.54 per month
Pioglitazone	9.42	BNF 69	Assuming 536mg (800IU) daily – £1.57 per month

N.2.3.7.3 Health states

Health state costs were constructed with GDG guidance so they represent a reference patient pathway. The main assumption was that non-NASH patients are managed in primary care while patients with more advanced liver disease are managed in secondary care settings. Health state costs include staff, test, procedure and drug costs where relevant. Staff costs were sourced from the NHS reference cost 2013/14 schedules and PSSRU 2014. Test costs were sourced from a relevant HTA

(Donnan 2009). Complication costs related to cirrhosis were sourced from an HTA on HCV patients (Wright 2006) and were assumed to be relevant to NAFLD patients. Liver transplant costs were assumed to be similar to those in Hepatitis B or C patients. Cost figures were sourced from Brown 2006 and Wright 2006.

Table 67: 6-monthly health state costs based on GDG guidance

Input	Value	Details
No NAFLD	variable	Dependent on the frequency of NAFLD testing
NAFL-NASH-F012	67	Assuming 80% of this health state have NAFLD and 20% have NASH
NAFL-NASH-F012 (treated)	167	Assuming 80% of this health state have NAFLD and 20% have NASH + lifestyle modification intervention
Fibrosis F3	216	same as compensated cirrhosis (NAFLD GDG suggestion)
Compensated cirrhosis	216	1 appointment with hepatologist +FBC+INR+LFT+ drug intervention costs
Fibrosis F3 (under lifestyle modification treatment)	316	same as compensated cirrhosis (NAFLD GDG suggestion)
Compensated cirrhosis (under lifestyle modification treatment)	316	1 appointment with hepatologist +FBC+INR+LFT+ drug and lifestyle modification interventions
Decompensated cirrhosis	6495.50	3 hepatologist appointments +FBC+LFT+INR+ complication costs
Bleeding	2653.19	1 non elective band ligation + 1.5 follow up band ligations
HCC	6495.50	Similar to those of decompensated cirrhosis state
Liver transplant – Year 1	29574.51	Average of HBV-HCV cohort costs
Liver transplant – Year 2	9185.77	Average of HBV-HCV cohort costs
Post-transplant	4198.03	Average of HBV-HCV cohort costs

N.2.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for other cause mortality.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities.

Where not already available, transition probabilities were calculated using an assumption of a fixed rate across each source-study follow up

Rates were converted into transition probabilities for the respective cycle length (6 months) before inputting into the Markov model. The probability of the event over the time horizon specified by the literature was converted into a rate, before being converted into a probability appropriate for the cycle length. The above conversions were done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (X months)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (6 months)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in each state of the model (6 months) was weighted by a utility value that is dependent on the time spent in the model and the treatment effect. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

In the deterministic and probabilistic analyses, the total number of QALYs and resource costs accrued by patients in every health state was recorded. These subtotals were summed across all subgroups to ascertain the total number of patients in the population and the total QALYs and resource costs accrued for the population. The total cost and QALYs accrued by the cohort was divided by the number of patients in the population to calculate a cost per patient and cost per QALY.

N.2.5 Model validation

The model was developed in consultation with the NAFLD and Cirrhosis GDGs; model structures, inputs and results were presented to and discussed with the GDGs for clinical validation and interpretation.

The models were systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The models were peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of many of the model calculations.

N.2.6 Estimation of cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost-effective if: • ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the

total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = (QALYs(X) \times \lambda) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy. The NMB figure is followed by the test ranking and the 95% confidence intervals of the ranks. An additional figure that represented the percentage of simulations where every test ranked first was also calculated.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown.

N.2.7 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[689] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several diagnostic tests, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained. Where the differences in the NMBs between alternative options were considered small ICERs were calculated to interpret the model results.

N.3 Results

As already discussed the NAFLD and advanced fibrosis models were run multiple times for different combinations of risk factors and retest frequencies. A list with all the combinations tested follows in Table 68. Base case results below were obtained from the probabilistic analysis to take combined parameter uncertainty into account. Results comparing the different frequencies of retesting were obtained from the deterministic sensitivity analysis.

Table 68: Model iterations

Model	Combinations
NAFLD	Metabolic syndrome – 1 to 6 years retesting
	Type 2 diabetes – 1 to 6 years retesting
	BMI>30 or high triglycerides – 5 years retesting
	Low HDL or wider waist circumference – 5 years retesting
	Type 2 diabetes – starting age 50, 55, 58 years (45 years used as basecase)
Advanced fibrosis	Base case prevalence – 3 years retesting
	Hypertension – 3 years retesting
	Base case prevalence – starting age 55, 60 years (50 years used as base case)

Cost-effectiveness is defined by the value of the net monetary benefit (NMB) attributed to every test.

The NAFLD model results are presented according to the level of NAFLD prevalence for every risk factor (from high to low). In the advanced fibrosis model, results are presented for only the base case prevalence and the hypertension group since they had the lowest and the highest prevalence and the model was not sensitive to the level of disease prevalence overall. At the end of the result section for each model a table is also presented comparing the cost-effectiveness of the first ranking test across different frequencies of testing.

N.3.1 NAFLD testing results

N.3.1.1 People with metabolic syndrome – 5 years retest frequency

Table 69: Number of events and time spent in health states

	Events (per patient)					Time spent (months)					
Test	**Transplants**	**Unexpected HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**CompFN++/VarFN++**	**Comp/Var-FN+**	**Comp**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar-Protected**
CAP at 200-249	0.007	0.010	0.051	0.039	0.235	0.29	2.22	19.43	1.89	0.67	4.36
Fatty liver index	0.007	0.014	0.048	0.041	0.238	2.15	2.16	18.02	1.94	0.63	4.17
MRI PDFF at 6.87	0.007	0.014	0.048	0.041	0.239	2.47	2.17	17.74	1.95	0.62	4.16
MRS at 0-5	0.007	0.011	0.051	0.039	0.236	0.47	2.25	19.29	1.89	0.66	4.35
Ultrasound	0.007	0.013	0.049	0.040	0.237	1.62	2.17	18.47	1.93	0.64	4.20
LFS at 0.16	0.007	0.016	0.047	0.042	0.240	3.28	2.09	17.16	1.97	0.60	4.05
Steatotest at 0.38	0.007	0.011	0.051	0.039	0.235	0.41	2.20	19.36	1.89	0.66	4.34
Liver biopsy	0.007	0.007	0.055	0.037	0.233	0.03	0.91	20.66	1.85	0.70	4.81
No test – treat all	0.007	0.010	0.052	0.039	0.235	0.00	2.28	19.60	1.88	0.67	4.41
No test – no treatment	0.009	0.055	0.011	0.063	0.267	25.82	0.00	0.05	2.48	0.14	2.18

Table 70: Life years and results

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
CAP at 200-249	32.80	7,630	15.36	299,668	7	3	9	0.002	7
Fatty liver index at 60	32.74	6,703	15.34	300,007	1	1	9	0.339	1
MRI PDFF at 6.87	32.74	6,762	15.33	299,880	4	1	10	0.195	2
MRS at 0-5	32.79	7,325	15.36	299,825	5	1	8	0.036	5

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
Ultrasound	32.75	6,849	15.34	299,926	2	1	8	0.054	4
LFS at 0.16	32.71	6,570	15.32	299,900	3	1	9	0.127	3
Steatotest at 0.38	32.80	7,586	15.36	299,674	6	3	9	0.001	6
Liver biopsy	32.83	8,175	15.38	299,386	9	1	10	0.028	9
No test – treat all	32.81	7,966	15.37	299,489	8	5	10	0.000	8
No test – no treatment	32.28	3,953	15.16	299,238	10	1	10	0.220	10

N.3.1.2 People with type 2 diabetes – 5 years retest frequency

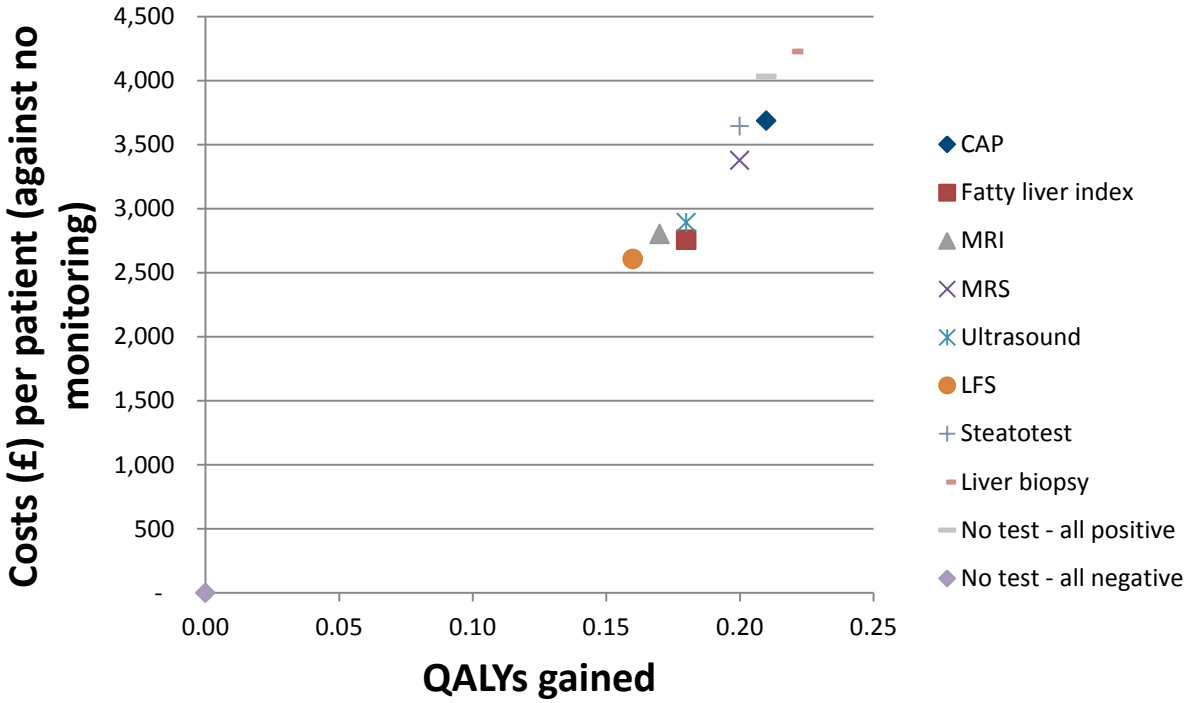
Table 71: Number of events and time spent in health states

	Events (per patient)					Time spent (months)					
Test	Transplants	Unexpected HCCs	Expected HCCs	Bleedings	Liver deaths	CompFN++/VarFN++	Comp/Var-FN+	Comp	Decomp	var+dcVar - Unprotected	var+dcVar - Protected
CAP at 200-249	0.007	0.010	0.051	0.039	0.233	0.28	2.21	19.30	1.87	0.66	4.32
Fatty liver index at 60	0.007	0.014	0.048	0.041	0.236	2.09	2.15	17.93	1.92	0.62	4.13
MRI PDFF at 6.87	0.007	0.014	0.047	0.041	0.237	2.46	2.16	17.61	1.93	0.62	4.12
MRS at 0-5	0.007	0.011	0.051	0.039	0.234	0.45	2.24	19.17	1.88	0.66	4.31
Ultrasound	0.007	0.013	0.049	0.040	0.235	1.62	2.16	18.33	1.91	0.64	4.16
LFS at 0.16	0.007	0.016	0.046	0.042	0.238	3.33	2.07	16.99	1.95	0.60	4.01
Steatotest at 0.38	0.007	0.010	0.051	0.039	0.233	0.40	2.18	19.23	1.87	0.66	4.30
Liver biopsy	0.007	0.007	0.055	0.036	0.232	0.03	0.92	20.51	1.84	0.70	4.76
No test – treat all	0.007	0.010	0.051	0.038	0.233	0.00	2.26	19.47	1.86	0.67	4.37
No test – no treatment	0.009	0.054	0.011	0.063	0.265	25.64	0.00	0.05	2.45	0.14	2.16

Table 72: Life years and results

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
CAP at 200-249	32.85	7,588	15.39	300,140	7	3	9	0.002	7
Fatty liver index at 60	32.79	6,658	15.36	300,497	1	1	8	0.336	1
MRI PDFF at 6.87	32.78	6,704	15.35	300,370	4	1	10	0.207	2
MRS at 0-5	32.84	7,277	15.38	300,305	5	1	8	0.036	5
Ultrasound	32.80	6,793	15.36	300,410	2	1	8	0.052	4
LFS at 0.16	32.75	6,507	15.34	300,383	3	1	9	0.120	3
Steatotest at 0.38	32.84	7,544	15.38	300,147	6	3	9	0.001	6
Liver biopsy	32.87	8,127	15.40	299,842	9	2	10	0.021	9
No test – treat all	32.86	7,932	15.39	299,953	8	6	10	0.000	8
No test – no treatment	32.33	3,902	15.18	299,764	10	1	10	0.226	10

Figure 389: Cost-effectiveness plot: people with type 2 diabetes at 5 years retesting frequency



Across the 8 different tests compared in the NAFLD model the fatty liver index ranked higher with a NMB of £300,497. FLI was followed by ultrasound and the liver fat score that had NMB figures of £300,410 and £300,383 respectively. Compared to FLI, ultrasound delivered almost identical QALYs at an incremental cost of £135 per patient. LFS had the lowest mean costs across all tests but delivered fewer QALYs compared to FLI and ultrasound. MRI was dominated by FLI being more costly and less effective while MRS, Steatotest and CAP delivered more QALYs than FLI but at much higher costs. Across all tests, liver biopsy delivered the highest number of QALYs but for a substantial incremental cost of £1,469 compared to FLI. The confidence intervals in the

rankings only excluded CAP, Steatotest and liver biopsy from ranking first, demonstrating the level of uncertainty in the cost-effectiveness of the remaining strategies. See also Figure 389 above.

N.3.1.3 Frequency of testing – 1 to 6 years

Table 73: Metabolic syndrome – results for FLI per frequency scenario (deterministic)

Retest frequency	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY
1 year	7,725	15.27	297,724
2 years	7,424	15.27	297,941
3 years	7,180	15.26	297,990
4 years	7,068	15.26	298,073
5 years	6,957	15.25	**298,116**
6 years	6,813	15.24	298,074

Table 74: Type 2 diabetes – results for FLI per frequency scenario (deterministic)

Retest frequency	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY
1 year	7,676	15.30	298,231
2 years	7,370	15.29	298,453
3 years	7,123	15.28	298,506
4 years	7,009	15.28	298,590
5 years	6,898	15.28	**298,634**
6 years	6,752	15.27	298,593

Testing for NAFLD using FLI was cost-effective compared to no testing for all retest frequencies. The NMB of FLI however varied across the different retest frequencies. For both type 2 diabetes and the metabolic syndrome cohorts (as well as the rest of the model cohorts – not presented here), the 5-year retest frequency delivered the highest NMB. The ICERs for 5-year retesting compared to 6-year retesting were £15,534 and £15,682 per QALY for the metabolic syndrome and the type 2 diabetes cohorts respectively (that is, below £20,000 per QALY). The ICERs for 4-year retesting compared to 5-year retesting were £32,601 and £32,861 per QALY for the metabolic syndrome and the type 2 diabetes cohorts respectively (that is, above £20,000 per QALY).

N.3.1.4 People with BMI>30 or high triglycerides – 5 years retest frequency

Table 75: Life years and results

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
CAP at 200-249	33.18	7,250	15.55	303,726	7	4	9	0.001	7
Fatty liver index at 60	33.12	6,260	15.52	304,156	1	1	8	0.329	1
MRI PDFF at 6.87	33.12	6,273	15.52	304,041	4	1	9	0.203	2
MRS at 0-5	33.17	6,882	15.54	303,932	5	1	8	0.031	5
Ultrasound	33.13	6,391	15.52	304,069	2	1	7	0.061	4
LFS at 0.16	33.09	6,129	15.51	304,057	3	1	9	0.124	3
Steatotest at 0.38	33.17	7,207	15.55	303,734	6	4	9	0.000	6
Liver biopsy	33.19	7,754	15.55	303,318	10	3	10	0.006	10
No test – treat all	33.19	7,639	15.56	303,494	9	6	10	0.000	8
No test – no treatment	32.70	3,603	15.36	303,551	8	1	10	0.246	9

N.3.1.5 People with low HDL or wide waist circumference – 5 years retest frequency

Table 76: Life years and results

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic result)
CAP at 200-249	33.65	6,754	15.77	308,741	8	4	9	0.000	8
Fatty liver index at 60	33.60	5,674	15.75	309,286	1	1	6	0.313	1
MRI PDFF at 6.87	33.59	5,667	15.74	309,188	3	1	9	0.188	2
MRS at 0-5	33.64	6,314	15.77	309,004	5	2	8	0.023	5
Ultrasound	33.61	5,811	15.75	309,188	4	1	6	0.060	4

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic result)
LFS at 0.16	33.57	5,550	15.74	309,197	2	1	8	0.121	3
Steatotest at 0.38	33.65	6,718	15.77	308,750	7	4	9	0.000	7
Liver biopsy	33.64	7,203	15.77	308,174	10	5	10	0.001	10
No test – treat all	33.66	7,210	15.78	308,444	9	7	10	0.000	9
No test – no treatment	33.23	3,159	15.60	308,891	6	1	10	0.295	6

N.3.1.6 Effect of increasing starting age

Table 77: Life years and results: people with type 2 diabetes, starting age 50 years

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
CAP at 200-249	29.27	6,877	14.46	282,316	7	3	9	0.001	7
Fatty liver index at 60	29.23	5,995	14.43	282,685	1	1	8	0.331	1
MRI PDFF at 6.87	29.22	6,047	14.43	282,552	4	1	10	0.150	2
MRS at 0-5	29.27	6,584	14.45	282,465	5	1	8	0.026	5
Ultrasound	29.23	6,113	14.44	282,599	3	1	7	0.053	4
LFS at 0.16	29.20	5,854	14.42	282,600	2	1	9	0.116	3
Steatotest at 0.38	29.27	6,832	14.46	282,326	6	4	9	0.001	6
Liver biopsy	29.30	7,424	14.47	282,003	10	2	10	0.019	10
No test – treat all	29.28	7,210	14.47	282,130	9	6	10	0.000	9
No test – no treatment	28.90	3,485	14.29	282,281	8	1	10	0.304	8

Table 78: Life years and results: people with type 2 diabetes, starting age 55 years

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
CAP at 200-249	25.63	6,100	13.38	261,448	8	4	9	0.000	8
Fatty liver index at 60	25.60	5,262	13.35	261,829	1	1	7	0.313	1
MRI PDFF at 6.87	25.60	5,348	13.35	261,689	5	1	9	0.094	3
MRS at 0-5	25.62	5,826	13.37	261,585	6	2	8	0.016	6
Ultrasound	25.60	5,376	13.36	261,740	3	1	6	0.043	4
LFS at 0.16	25.58	5,136	13.35	261,765	2	1	9	0.109	2
Steatotest at 0.38	25.63	6,057	13.38	261,462	7	4	9	0.001	7
Liver biopsy	25.65	6,670	13.39	261,100	10	3	10	0.012	10
No test – treat all	25.64	6,425	13.38	261,266	9	6	10	0.000	9
No test – no treatment	25.37	3,027	13.24	261,710	4	1	10	0.413	5

Table 79: Life years and results: people with type 2 diabetes, starting age 58 years

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
CAP at 200-249	23.44	5,625	12.65	247,438	8	4	9	0.000	8
Fatty liver index at 60	23.41	4,815	12.63	247,820	2	1	6	0.287	1
MRI PDFF at 6.87	23.41	4,906	12.63	247,671	5	1	9	0.063	4
MRS at 0-5	23.43	5,368	12.65	247,563	6	2	8	0.011	6
Ultrasound	23.41	4,930	12.63	247,730	4	1	6	0.036	5
LFS at 0.16	23.40	4,706	12.62	247,776	3	1	8	0.104	2
Steatotest at 0.38	23.44	5,583	12.65	247,454	7	4	9	0.000	7
Liver biopsy	23.46	6,204	12.66	247,071	10	4	10	0.008	10

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
No test – treat all	23.44	5,942	12.66	247,259	9	7	10	0.000	9
No test – no treatment	23.24	2,753	12.53	247,838	1	1	10	0.489	3

N.3.2 Advanced fibrosis testing

N.3.2.1 People with NAFLD, base case prevalence – 3 years retest frequency

Table 80: Number of events and time spent in health states

	Events (per patient)					Time spent (months)				
Test	Transplants	Unexpected HCCs	Expected HCCs	Bleedings	Liver deaths	Comp/Var-FN+	Comp	Decomp	var+dcVar - Unprotected	var+dcVar - Protected
APRI at 0.98–1	0.009	0.013	0.067	0.054	0.294	3.34	24.24	2.38	0.84	6.36
ARFI at 4.24	0.009	0.008	0.072	0.051	0.291	0.86	26.29	2.32	0.90	6.72
AST/ALT at 0.8	0.009	0.009	0.070	0.052	0.290	1.48	25.53	2.31	0.88	6.48
BARD at 2	0.009	0.008	0.071	0.051	0.289	0.87	26.01	2.29	0.89	6.59
ELF at 10.51	0.009	0.009	0.071	0.052	0.293	1.61	25.83	2.36	0.89	6.69
Ferritin at 2x	0.010	0.034	0.047	0.066	0.308	14.29	15.14	2.65	0.59	5.00
FIB4 at 1.45	0.009	0.007	0.072	0.050	0.289	0.44	26.36	2.29	0.90	6.68
FibroTest at 0.47	0.009	0.012	0.068	0.054	0.295	3.22	24.43	2.39	0.85	6.44
MRE at 4.15	0.009	0.009	0.071	0.052	0.292	1.35	25.96	2.34	0.89	6.69

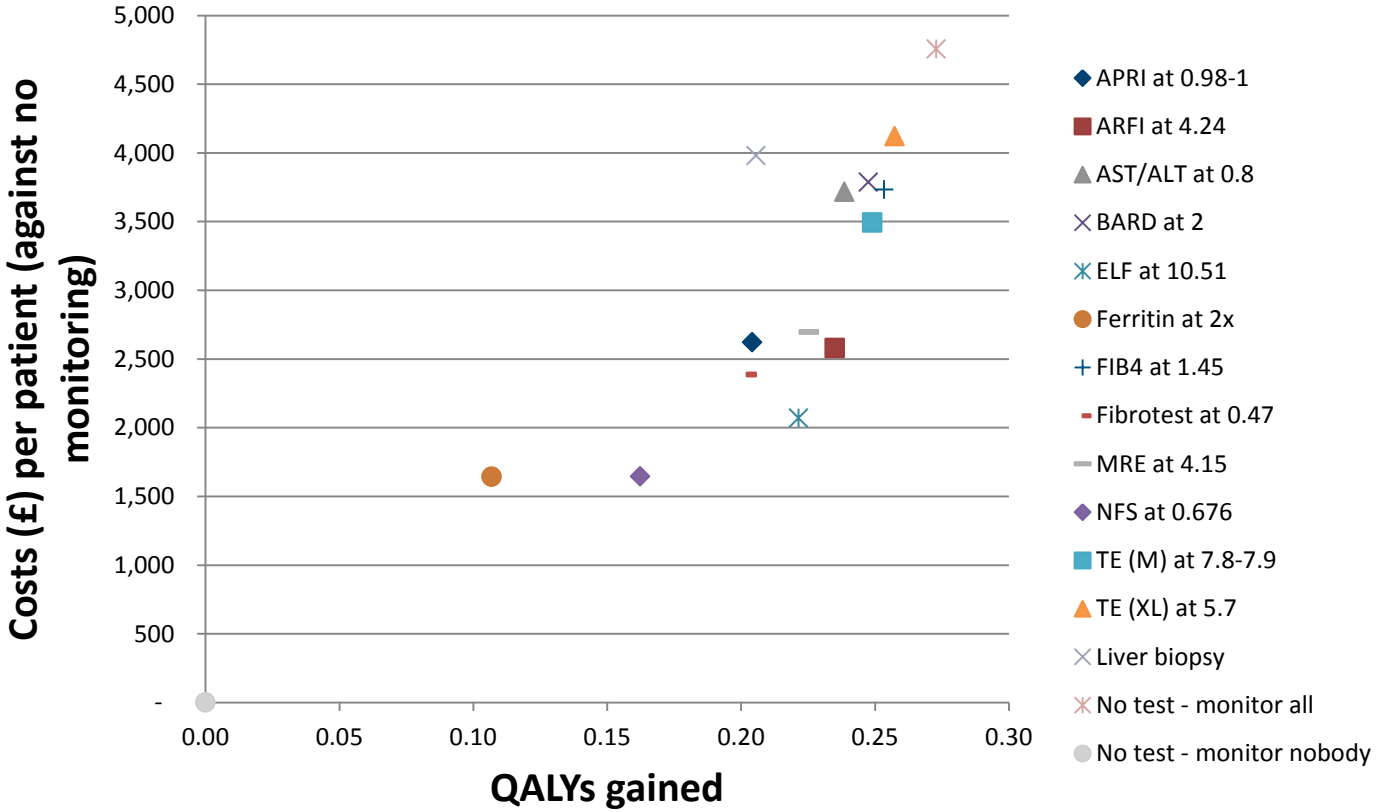
	Events (per patient)					Time spent (months)				
Test	**Transplants**	**Unexpected HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**Comp/Var-FN+**	**Comp**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar - Protected**
NFS at 0.676	0.010	0.019	0.062	0.058	0.300	6.87	21.52	2.49	0.77	6.07
TE (M) at 7.8–7.9	0.009	0.007	0.072	0.050	0.289	0.51	26.38	2.29	0.90	6.70
TE (XL) at 5.7	0.009	0.007	0.072	0.050	0.288	0.40	26.35	2.28	0.90	6.66
Liver biopsy	0.009	0.006	0.074	0.050	0.291	0.36	26.79	2.32	0.93	6.98
No test - monitor all	0.009	0.006	0.072	0.049	0.287	0.00	26.54	2.26	0.90	6.71
No test - monitor nobody	0.012	0.068	0.014	0.085	0.330	32.32	0.06	3.06	0.17	2.93

Table 81: Life years and results

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
APRI at 0.98–1	27.33	10,184	13.68	263,403	7	3	12	0.0008	6
ARFI at 4.24	27.40	10,142	13.71	264,060	2	1	6	0.1714	2
AST/ALT at 0.8	27.41	11,280	13.71	262,996	10	6	13	0	10
BARD at 2	27.43	11,350	13.72	263,105	9	5	13	0	9
ELF at 10.51	27.37	9,632	13.70	264,301	1	1	11	0.7302	1
Ferritin at 2x	27.07	9,206	13.58	262,433	13	5	14	0	13
FIB4 at 1.45	27.45	11,295	13.73	263,277	8	3	11	0.001	8

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
FibroTest at 0.47	27.33	9,949	13.68	263,596	4	3	11	0.0008	4
MRE at 4.15	27.38	10,259	13.70	263,751	3	2	10	0.012	3
NFS at 0.676	27.22	9,208	13.64	263,541	5	2	13	0.0152	5
TE (M) at 7.8–7.9	27.44	11,056	13.72	263,426	6	2	12	0.0158	7
TE (XL) at 5.7	27.46	11,685	13.73	262,964	11	6	14	0	11
Liver biopsy	27.33	11,543	13.68	262,071	14	7	15	0	14
No test - monitor all	27.49	12,319	13.75	262,641	12	6	15	0.0002	12
No test - monitor nobody	26.76	7,563	13.48	261,939	15	1	15	0.0526	15

Figure 390: Cost-effectiveness plot: base case prevalence at 3 year retest frequency



Across the 15 different strategies compared in the advanced fibrosis model ELF ranked higher with a NMB of £264,301. It was followed by ARFI and MRE, which had NMBs of £264,060 and £263,751 respectively. Compared to ELF, ARFI delivered 0.01 more QALYs for an incremental cost of £510 per patient. MRE delivered similar QALYs with ELF for an incremental cost of £627. FibroTest was dominated by ELF as it was more costly and less effective. NFS was less costly compared to ELF but also considerably less effective. Transient elastography at 7.8–7.9 was more effective than ELF but for an incremental cost of £1,424. In the confidence intervals accompanying the strategy rankings it was only ELF, ARFI and the 'no test – monitor nobody' strategy that had the

first rank within their low confidence intervals. However, the latter had an extremely wide CI (first to last place). ELF also had the best performance probabilistically, ranking first in 73% of the 5,000 simulations. ARFI followed, ranking first in 17% of the simulations.

N.3.2.2 People with NAFLD and hypertension – 3 years retest frequency

Table 82: Life years and results

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
APRI at 0.98–1	25.47	12,432	12.63	240,252	9	4	13	0.0002	9
ARFI at 4.24	25.58	12,462	12.68	241,175	2	1	6	0.2062	2
AST/ALT at 0.8	25.56	13,308	12.67	240,123	11	6	13	0	11
BARD at 2	25.59	13,383	12.69	240,349	7	5	12	0	8
ELF at 10.51	25.55	12,081	12.67	241,285	1	1	13	0.725	1
Ferritin at 2x	25.13	11,532	12.50	238,560	14	8	14	0	14
FIB4 at 1.45	25.62	13,348	12.70	240,599	5	2	10	0.0024	5
FibroTest at 0.47	25.47	12,267	12.64	240,446	6	3	13	0.0004	6
MRE at 4.15	25.55	12,583	12.67	240,835	3	2	10	0.0136	3
NFS at 0.676	25.34	11,623	12.59	240,094	12	2	13	0.0026	12
TE (M) at 7.8–7.9	25.61	13,179	12.69	240,696	4	1	12	0.0266	4
TE (XL) at 5.7	25.62	13,666	12.70	240,338	8	5	13	0	7
Liver biopsy	25.54	13,707	12.67	239,633	13	5	15	0	13
No test - monitor all	25.66	14,145	12.72	240,208	10	3	15	0.0028	10

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
No test - monitor nobody	24.77	10,080	12.38	237,516	15	2	15	0.0202	15

N.3.2.3 Frequency of advanced fibrosis testing – 1 to 6 years

Table 83: NAFLD base case prevalence – results for ELF per frequency scenario (deterministic)

Combinations	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY
1 year	10,694	13.64	262,202
2 years	9,988	13.63	262,589
3 years	9,672	13.61	**262,605**
4 years	9,428	13.60	262,574
5 years	9,268	13.59	262,480
6 years	9,114	13.58	262,399

Testing for advanced fibrosis using ELF was cost-effective compared to no testing for all retest frequencies. However, the NMB of ELF varied across the different frequencies. The 3-year retest frequency delivered the highest NMB, followed closely by 2 years. The ICER for 3-year retesting compared to 4-year retesting was £17,740, but the ICER for 2-year retesting compared to 3-year retesting was £21,082 per QALY.

N.3.2.4 Effect of increasing starting age

Table 84: Life years and results: people with NAFLD (base case prevalence), starting age 55 years

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
APRI at 0.98–1	24.13	9,212	12.71	245,081	6	3	11	0.0008	6
ARFI at 4.24	24.19	9,176	12.74	245,652	2	1	7	0.1524	2
AST/ALT at 0.8	24.20	10,267	12.74	244,595	10	6	14	0.0000	10

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
BARD at 2	24.21	10,338	12.75	244,686	9	6	13	0.0000	9
ELF at 10.51	24.17	8,709	12.73	245,888	1	1	10	0.7176	1
Ferritin at 2x	23.94	8,298	12.63	244,385	12	4	14	0.0000	12
FIB4 at 1.45	24.22	10,277	12.76	244,849	8	3	12	0.0004	8
FibroTest at 0.47	24.13	8,993	12.71	245,275	5	2	11	0.0028	5
MRE at 4.15	24.18	9,304	12.73	245,368	3	2	9	0.0106	3
NFS at 0.676	24.05	8,300	12.68	245,305	4	2	12	0.0156	4
TE (M) at 7.8–7.9	24.22	10,043	12.75	245,005	7	2	13	0.0164	7
TE (XL) at 5.7	24.23	10,661	12.76	244,527	11	6	14	0.0000	11
Liver biopsy	24.14	10,584	12.72	243,749	15	8	15	0.0000	15
No test - monitor all	24.26	11,293	12.77	244,170	14	7	15	0.0010	13
No test - monitor nobody	23.72	6,842	12.55	244,203	13	1	15	0.0824	14

Table 85: Life years and results: people with NAFLD (base case prevalence), starting age 60 years

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
APRI at 0.98–1	20.89	8,063	11.61	224,061	6	3	11	0.0006	6
ARFI at 4.24	20.93	8,023	11.63	224,545	2	1	7	0.1448	2
AST/ALT at 0.8	20.93	9,047	11.63	223,533	12	7	14	0.0000	12

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic results)
BARD at 2	20.95	9,124	11.64	223,597	11	6	13	0.0000	10
ELF at 10.51	20.92	7,628	11.62	224,778	1	1	8	0.6938	1
Ferritin at 2x	20.74	7,239	11.54	223,610	10	4	14	0.0000	11
FIB4 at 1.45	20.95	9,065	11.64	223,746	8	4	12	0.0000	8
FibroTest at 0.47	20.89	7,866	11.61	224,248	5	2	9	0.0018	5
MRE at 4.15	20.92	8,168	11.62	224,275	4	2	9	0.0076	4
NFS at 0.676	20.83	7,236	11.58	224,352	3	1	12	0.0268	3
TE (M) at 7.8–7.9	20.95	8,849	11.64	223,902	7	2	13	0.0162	7
TE (XL) at 5.7	20.96	9,439	11.64	223,425	13	7	14	0.0000	13
Liver biopsy	20.89	9,416	11.61	222,762	15	8	15	0.0000	15
No test - monitor all	20.98	10,055	11.65	223,039	14	9	15	0.0000	14
No test - monitor nobody	20.60	5,994	11.48	223,653	9	1	15	0.1084	9

N.3.3 Deterministic sensitivity analyses

N.3.3.1 Testing for NAFLD

Table 86: NAFLD model - Cost-effectiveness rank under different scenarios (people with type 2 diabetes tested every 5 years) – part 1

Tests	Basecase-diabetes	GP appointments: +1 for each test	Other-cause mortality: +50%	Other-cause mortality: +100%	Liver-related mortality: -25%	Liver-related mortality: -50%	TP no NAFLD→ NAFLD (F012):-25%	TP no NAFLD→ NAFLD (F012):-50%	TP F012→ F3: -25%	TP F012→ F3: -50%	TP F3 →comp cirr: -25%	TP F3 →comp cirr: -50%	TP compcirr→ decomp: -25%	TP compcirr→ decomp: -50%
CAP at 200-249	7	7	7	7	7	7	7	7	7	8	8	8	7	8
Fatty liver index	1	1	1	1	1	1	1	2	1	2	1	2	1	1
MRI PDFF at 6.87	2	2	2	2	2	2	2	1	2	4	2	4	2	2
MRS at 0-5	5	5	5	5	5	5	5	5	5	6	5	6	5	5
Ultrasound	4	4	4	4	4	4	4	4	4	5	4	5	4	4
LFS	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Steatotest	6	6	6	6	6	6	6	6	6	7	7	7	6	7
Liver biopsy	9	9	10	10	9	9	9	10	10	10	10	10	10	10
No test – treat all	8	8	8	9	8	8	8	8	9	9	9	9	8	9
No test – no treatment	10	10	9	8	10	10	10	9	8	1	6	1	9	6

Table 87: NAFLD model - Cost-effectiveness rank under different scenarios (people with type 2 diabetes tested every 5 years) – part 2

Tests	Basecase-diabetes	Lifestyle modification intervention: OFF	Lifestyle modification intervention: effectiveness +100%	Unit cost FLI: -25%	Unit cost FLI: +25%	Unit cost Ultrasound: -25%	Unit cost ultrasound: +25%	Discount rate: 1.5%	Diagnostic accuracy FLI: low CI for sens	Diagnostic accuracy FLI: low CI for spec	Diagnostic accuracy FLI: low CI for sens and spec	Advanced fibrosis test: ARFI instead of ELF	Liver-related mortality: -50% / other-cause mortality: +50% / TP No NAFLD to F012, F012 to F3, F3 to F4: -20%	Starting age 58 / +1 GP appointments per test	Starting age 58 / +1 GP appointments per test / without lifestyle modification intervention
CAP at 200-249	7	8	7	7	7	7	7	6	7	7	7	8	8	8	8
Fatty liver index	1	2	1	1	1	1	1	2	1	5	5	2	1	2	2
MRI PDFF at 6.87	2	1	2	2	2	2	2	1	2	1	1	1	4	4	4
MRS at 0-5	5	5	5	5	5	5	5	5	5	4	4	5	6	6	6
Ultrasound	4	4	4	4	4	4	4	4	4	3	3	4	5	5	5
LFS	3	3	3	3	3	3	3	3	3	2	2	3	3	3	3
Steatotest	6	7	6	6	6	6	6	7	6	6	6	7	7	7	7
Liver biopsy	9	10	9	9	9	9	9	8	9	9	9	9	10	10	10
No test – treat all	8	9	8	8	8	8	8	9	8	8	8	10	9	9	9
No test – no treatment	10	6	10	10	10	10	10	10	10	10	10	6	2	1	1

In 17 out of 27 tested scenarios FLI remained first in ranking. It came second and fifth in the remaining 10 scenarios. MRI was second in most scenarios. LFS remained third in all scenarios apart from where the FLI diagnostic sensitivity was set at its low CI (ranked second). The 'no test – no treatment' strategy ranked first in the scenarios where 58 years was set as the starting age and the scenarios where the transition probabilities of F012 → F3 or F3→ compcirr were reduced by 50%.

N.3.3.2 Testing for advanced fibrosis

Table 88: Advanced fibrosis model - Cost-effectiveness rank under different scenarios (people with NAFLD tested every 3 years) – part 1

Tests	Base case	ELF unit cost: -25%	ELF unit cost: +25%	Other-cause mortality: +50%	Other-cause mortality: +100	Liver-related mortality: -25%	Liver-related mortality: -50%	TP F012→ F3: -25%	TP F012→ F3: -50%	TP F3→ compcirr: -25%	TP F3→ compcirr: - 50%
APRI at 0.98–1	6	6	6	6	6	6	7	6	6	6	7
ARFI at 4.24	2	2	2	2	2	2	2	2	2	2	3
AST/ALT at 0.8	10	10	10	10	10	11	11	10	12	10	12
BARD at 2	9	9	9	9	9	9	9	9	11	9	11
ELF at 10.51	1	1	1	1	1	1	1	1	1	1	1
Ferritin at 2x	13	13	13	12	12	13	13	12	9	12	8
FIB4 at 1.45	8	8	8	8	8	8	8	8	10	8	10
FibroTest at 0.47	4	4	4	4	5	4	4	5	5	5	4
MRE at 4.15	3	3	3	3	3	3	3	3	4	3	5
NFS at 0.676	5	5	5	5	4	5	5	4	3	4	2
TE (M) at 7.8–7.9	7	7	7	7	7	7	6	7	8	7	9
TE (XL) at 5.7	11	11	11	11	11	10	10	11	13	11	13
Liver biopsy	14	14	14	15	15	14	14	15	15	15	15

Tests	Base case	ELF unit cost: -25%	ELF unit cost: +25%	Other-cause mortality: +50%	Other-cause mortality: +100	Liver-related mortality: -25%	Liver-related mortality: -50%	TP F012→ F3: -25%	TP F012→ F3: -50%	TP F3→ compcirr: -25%	TP F3→ compcirr: - 50%
No test - monitor all	12	12	12	13	14	12	12	14	14	14	14
No test - monitor nobody	15	15	15	14	13	15	15	13	7	13	6

Table 89: Advanced fibrosis model - Cost-effectiveness rank under different scenarios (people with NAFLD tested every 3 years) – part 2

Tests	Drug treatment: OFF	Drug treatment effectiveness: -33%	Drug treatmenteffectiveness: +33%	Discount rate: 1.5%	ELF diagnostic accuracy: low CI for sens	ELF diagnostic accuracy: low CI for spec	ELF diagnostic accuracy: low CIs for sens and spec	Cirrhosis test: ARFI instead of TE
APRI at 0.98–1	6	6	11	7	6	6	6	6
ARFI at 4.24	7	7	2	2	1	2	1	2
AST/ALT at 0.8	11	10	9	11	10	10	10	10
BARD at 2	12	12	8	9	9	9	9	9
ELF at 10.51	4	4	1	1	2	1	4	1
Ferritin at 2x	2	2	14	14	13	13	13	13
FIB4 at 1.45	10	11	3	6	8	8	8	8
FibroTest at 0.47	5	5	10	4	4	4	3	4

Tests	Drug treatment: OFF	Drug treatment effectiveness: -33%	Drug treatmenteffectiveness: +33%	Discount rate: 1.5%	ELF diagnostic accuracy: low CI for sens	ELF diagnostic accuracy: low CI for spec	ELF diagnostic accuracy: low CIs for sens and spec	Cirrhosis test: ARFI instead of TE
MRE at 4.15	8	8	5	3	3	3	2	3
NFS at 0.676	3	3	13	8	5	5	5	5
TE (M) at 7.8–7.9	9	9	4	5	7	7	7	7
TE (XL) at 5.7	13	13	7	10	11	11	11	11
Liver biopsy	15	14	12	13	14	14	14	14
No test - monitor all	14	15	6	12	12	12	12	12
No test - monitor nobody	1	1	15	15	15	15	15	15

In 15 out of the 19 tested scenarios ELF remained first in the rankings. In the scenarios when ELF's sensitivity was set at its low CI it ranked second and fourth with ARFI ranking first. When the drug intervention was removed from the model or when its effectiveness was reduced, no testing ranked first. ARFI consistently ranked second (or higher) apart from when the progression rate to cirrhosis was decreased by 50% and the same 2 scenarios with the reduced drug effectiveness.

N.4 Discussion

N.4.1 Summary of results

N.4.1.1 NAFLD model

According to the present model, testing for NAFLD was considered cost-effective at a £20,000 per QALY threshold. Among the 8 diagnostic tests compared, FLI ranked first carrying the best combination of test unit costs and diagnostic accuracy. Ultrasound ranked second having lower sensitivity (64% against FLI's 76%) and noticeably higher test unit costs. LFS closely followed ultrasound with a slightly lower NMB. MRI and MRS ranked fourth and fifth across all tests having the highest diagnostic accuracy but for a considerably higher test unit cost. Most of these tests had similarly wide 95% confidence intervals ranking from first to eighth. When the starting age of the model was increased from 45 years to 50, 55, 58 years, the cost-effectiveness of testing dropped compared to no testing, with FLI having an ICER of £20,176 per QALY gained in the type 2 diabetes cohort at a 58 years starting age.

Testing for NAFLD was cost-effective compared to no testing at all retest frequencies. Irrespective of the risk factor examined, the 5-year retest frequency delivered the highest NMB benefit for FLI, though the difference in NMB at different frequencies was small nd within the margin of error.

In the deterministic sensitivity analysis, FLI remained the first ranking test in most of the examined scenarios. It came second to MRI and no testing when liver disease progression rates were decreased by 50%. MRI also came first when lifestyle modification intervention was removed, when the discount rate was set at 1.5% and when ARFI was set as the test for advanced fibrosis. In the multiway deterministic analysis FLI remained first when parallel changes were applied on the liver-related mortality, the other-cause mortality and the liver disease progression. No testing ranked first in the scenarios when the starting age was set at 58 years.

N.4.1.2 Advanced fibrosis model

Testing for advanced fibrosis was shown to be cost-effective for all risk groups and retest frequencies used in the model. Across the different retest frequencies the NMB of the first ranked test was greatest at a 3 year retest frequency, though the difference in NMB as the frequency changed was small.

Among the 15 diagnostic strategies included in the model, ELF ranked first having the highest diagnostic accuracy across the compared tests but also the second highest test unit costs. ARFI and MRE followed in terms of ranking having the next best diagnostic accuracies after ELF. FibroTest and NFS followed in fourth and fifth positions both having high specificity and low sensitivity; TE in contrast had high sensitivity and low specificity and ranked slightly lower. The results of the model appear to demonstrate that the most important factor in the ranking of the NILTs was their diagnostic accuracy characteristics, irrespective of their unit costs. There was considerable uncertainty in the results with all strategies having wide 95% confidence intervals apart from ARFI (first to sixth place).

In the deterministic sensitivity analyses, the rankings did not seem to be sensitive to changes in ELF's cost but they changed in favour of ARFI when ELF's sensitivity was set to its low CI. Removing the drug intervention or reducing its effectiveness by one third had a negative effect on the cost-effectiveness of testing with the 'no test – no treatment' strategy ranking first.

N.4.2 Generalisability to other populations or settings

Analyses in the present models were based on evidence relevant to an adult population. Extrapolations to children and young people are discussed thoroughly in the relevant 'Recommendations and link to evidence' sections of the full guideline document.

N.4.3 Comparisons with published studies

To our knowledge, the present modelling work is the first economic evaluation that addresses the cost-effectiveness of NAFLD and advanced fibrosis testing through cost-utility analyses using a lifetime pathway through liver disease. Comprehensive economic modelling in a NAFLD cohort has not been possible before mainly due to the lack of evidence around the early stages of the disease progression. This has been addressed in the present models with the use of recently published evidence that captured disease progression through studies with a paired liver biopsy design.

The only relevant studies that were identified in our literature search were 2 economic evaluations with a cost per correct diagnosis design in fibrosis testing. Steadman 2013[915] compared transient elastography with liver biopsy and Crossan 2015[226] compared a variety of non-invasive tests with liver biopsy.

Steadman concluded that liver biopsy was more costly and more effective compared to transient elastography with a cost per additional correct diagnosis of £846. In Crossan most testing strategies were dominated by cheap and relatively accurate options with liver biopsy having a cost per additional correct diagnosis of £49,627 and £140,610 for TPs and TNs respectively.

However, no safe conclusions can be made regarding the cost-effectiveness of the various fibrosis tests from these previous papers as important factors such as the follow-up costs and the health-related quality of life following correct or incorrect diagnoses have not been included in these 2 economic analyses.

N.4.4 Conclusions

- An original cost-utility analysis found that testing for NAFLD was cost-effective compared to no testing at a cost-effectiveness threshold of £20,000 per QALY for all retest frequencies and NAFLD prevalences investigated. Retesting at a frequency of 5 years was cost-effective compared to other frequencies. This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 10 different diagnostic strategies to detect NAFLD found that FLI ranked first compared to the following diagnostic strategies at a retest frequency of 5 years, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
    - ultrasound
    - NAFLD liver fat score
    - MRI PDFF
    - MRS
    - SteatoTest
    - CAP
    - no test – no treatment
    - liver biopsy
    - no test – treat all.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis found that testing adults with NAFLD for advanced fibrosis was cost-effective compared to no testing for all fibrosis prevalences and retest frequencies

investigated at a cost-effectiveness threshold of £20,000 per QALY gained. Retesting at a frequency of 3 years was cost-effective compared to other frequencies. This analysis was assessed as directly applicable with minor limitations.

- An original cost-utility analysis that compared 15 strategies for testing adults with NAFLD for advanced fibrosis, with a retest frequency of 3 years, found that ELF ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - ARFI
  - MRE
  - FibroTest
  - NAFLD fibrosis score
  - transient elastography (M probe)
  - APRI
  - FIB-4
  - BARD
  - AST-ALT ratio
  - transient elastography (XL probe)
  - no test – monitor all
  - ferritin
  - liver biopsy
  - no test – monitor nobody.

  This analysis was assessed as directly applicable with minor limitations.

Appendix O: Unit costs

O.1 Extra-hepatic conditions

Table 90: Unit costs of NHS secondary care appointments

Specialist	Cost of initial appointment	Cost of follow-up appointment	Source
Gastroenterologist	£162	£118	NHS reference costs 2013–14
Cardiologist	£160	£123	NHS reference costs 2013–14

O.2 Diet modification and supplements

Table 91: Unit costs of probiotic supplement

Test	Dose	Cost per month	Source
VSL#3	4.4 g daily	£33.89	BNF October 2015

O.3 Pharmacological interventions

Table 92: Unit costs of medications

Test	Dose	Cost per month	Source
Vitamin E	30 mg daily	£8.54	NHS hospital trust - GDG source
Pioglitazone	536 mg (800 international units) daily	£1.57	BNF October 2015

Appendix P: Research recommendations

P.1 Non-invasive tests for diagnosing NASH

Research question: Which non-invasive tests most accurately identify non-alcoholic steatohepatitis (NASH) in people with non-alcoholic fatty liver disease (NAFLD)?

Why this is important: NASH develops in only a minority of people with NAFLD. It is thought to be the precursor of liver fibrosis, which is associated with morbidity and mortality. As a result, NASH has been the main target for treatment in NAFLD. This is because reducing the severity of NASH would reduce the risk of a person progressing to fibrosis and advanced liver disease. However, the only way to identify people with NASH who would be suitable for treatments is by performing an invasive liver biopsy and assessing the risk to health and cost. Given that between 20% and 30% of the population have NAFLD, it is important that we have a simple non-invasive method for determining which of these people have NASH. Then they can start the treatment to prevent them from developing fibrosis and end-stage complications of liver disease.

Criteria for selecting high-priority research recommendations

PICO question	**Population:** People with NAFLD. **Index test:** Non-invasive tests to determine which patients have non-alcoholic steatohepatitis (NASH) including blood tests and various imaging techniques. **Reference standard:** Liver biopsy. **Outcomes:** Sensitivity, specificity, ROC curve or area under the curve (AUC).
Importance to patients or the population	The importance to patients would be identifying those patients with NAFLD who also have NASH and so could then be offered various treatments specific to patients with NASH to prevent them from developing advanced stages of liver disease.
Relevance to NICE guidance	An answer to this question would change NICE guidance in that non-invasive assessment of patients with NAFLD would include a test for NASH as well as the currently recommended test for identifying those with advanced fibrosis. The GDG has recommended treatment for people with advanced fibrosis diagnosed non-invasively since the vast majority of these people will have NASH and people with advanced fibrosis have the worst prognosis. This strategy will however 'miss' people with NASH without advanced fibrosis who will therefore also miss the benefit from treatment prior to developing advanced fibrosis. Clearly it would be preferable, subject to cost-effectiveness, to prevent the development of advanced fibrosis rather than only to treat the underlying NASH once this has developed. This will only be practical and feasible once a reliable non-invasive test for NASH has been developed.
Relevance to the NHS	An answer to this question would significantly reduce the need for liver biopsy in patients with suspected NASH and enable those patients with NASH to benefit from treatment and reduce their risk of developing the complications of end-stage liver disease.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework.
Current evidence base	The current evidence is considered in Chapter 7 of the full guideline. At present there are no reliable non-invasive tests that differentiate people with NAFLD with and without NASH.
Equality	No issues other than NAFLD and NASH being particularly common in people of South Asian family origin.
Study design	The study design would involve assessing various non-invasive blood tests and imaging methods in people with NAFLD with and without biopsy-proven NASH. Tests would be evaluated by standard methods including the construction of

	receiver operator curves (ROCs), specificities, sensitivities and diagnostic accuracies.
Feasibility	NAFLD is highly prevalent and the presence of NASH in these patients is high enough to design a suitably powered study to assess non-invasive tests in a reasonably short period of time; perhaps no more than a 2-year study.
Other comments	The trial may attract commercial funders in the diagnostics arena including companies developing novel blood tests as well as those developing imaging hardware and software.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.2 Non-invasive tests for diagnosing NAFLD and advanced liver fibrosis in children and young people

Research question: Which non-invasive tests most accurately diagnose NAFLD and advanced liver fibrosis in children and young people?

Why this is important: NAFLD has become the most common chronic liver disease in children and young people in industrialised countries, mainly as a result of increasing obesity rates.

The presence of NAFLD in children and young people is often suspected in those presenting with abnormal liver tests or evidence of fatty changes on ultrasound. However, the full spectrum of NAFLD (from simple steatosis to steatohepatitis, fibrosis, cirrhosis and liver-related morbidity) can also be present in the absence of abnormal liver tests.

Early detection and assessment of severity of NAFLD would be beneficial to identify children and young people with potential silent progressive fatty liver disease. Diagnostic practice varies widely and includes clinical, biochemical and radiographic tests. The review of evidence in this guideline showed that very few diagnostic techniques have been assessed in children and young people and, although there is some evidence for ELF in diagnosing advanced liver fibrosis in children and young people with NAFLD, this was only from 1 study. Further research is therefore warranted to confirm the most accurate tests in this group of people.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Children and young people with suspected NAFLD. **Index test:** Non-invasive tests to determine which patients have NAFLD and which patients with confirmed NAFLD have advanced fibrosis. **Reference standard:** Liver biopsy. **Outcome:** Sensitivity, specificity, ROC or area under the curve (AUC).
Importance to patients or the population	The importance to children and young people would be early identification of those patients with NAFLD and those with NAFLD who also have advanced fibrosis and so could then be offered various lifestyle modification strategies as well as treatments specific to advanced fibrosis to prevent them from developing advanced stages of liver disease.
Relevance to NICE guidance	Further research on non-invasive diagnostic tests would allow NICE to issue clear guidance for diagnosis of children and young people with suspected NAFLD and a stronger evidence base for diagnosis of advanced fibrosis, that can be implemented at primary and secondary care levels and would inform recommendations for an update of this guidance.
Relevance to the NHS	An answer to this question would help increase confidence in diagnosing NAFLD in children and young people and those with NAFLD with suspected advanced fibrosis by the means of non-invasive tests. Additionally, it would allow introduction of various lifestyle modification strategies as well as treatments

	specific to advanced fibrosis at an earlier stage and thus reduce the risk of developing advanced stages of liver disease and reduce other health risks associated with NAFLD such as cardiovascular disease and type 2 diabetes.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework.
Current evidence base	The current evidence is considered in Chapters 6 and 7 of the full guideline. At present, for children and young people, there are no reliable non-invasive tests validated in this population to diagnose NAFLD and limited evidence for diagnosis of advanced fibrosis in those with NAFLD.
Equality	There are no equality issues.
Study design	The study would involve assessing various existing non-invasive blood tests and imaging methods in children and young people with suspected NAFLD and those with confirmed NAFLD where advanced fibrosis is suspected. Tests would be evaluated by standard methods including specificities, sensitivities, receiver operator curves (ROCs) or area under the curves (AUC). In order to recruit sufficient number of patients and as liver biopsy in children and young people is only carried out in the 3 national paediatric liver centres, this should be a multicentre study involving all 3 centres.
Feasibility	The prevalence of NAFLD in children and young people is high enough to design a suitably powered study to assess non-invasive tests in a reasonably short time period (1–2 year study).
Other comments	The study may attract commercial funders including companies developing novel blood tests as well as those developing imaging hardware and software.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.3 Probiotic and prebiotic supplements

Research question: What is the clinical and cost-effectiveness of using probiotics or prebiotics to treat NAFLD in children, young people and adults?

Why this is important: NAFLD is the most common metabolic liver disease occurring in approximately 30% of all adults, around 46% of obese people and around 53% of people with type 2 diabetes. Liver fat accumulation is the first stage of more serious chronic liver disease in NAFLD. A small body of evidence supports the use of probiotics in NAFLD but the data are inconclusive and the results of high quality double-blind randomised placebo-controlled trials are needed. The evidence from cross-sectional studies suggests associations between unfavourable disturbance in gut microbiota and obesity or type 2 diabetes, but there is very limited evidence on whether modifying the gut microbiota influences NAFLD.

Criteria for selecting high-priority research recommendations

PICO question	**Population:** People with NAFLD. **Intervention:** Probiotic, prebiotic or synbiotic (probiotic and prebiotic combined). **Comparison:** Placebo. **Outcomes:** • Progression or regression of NAFLD severity as assessed by: ○ Liver biopsy ○ MRI/MRS ○ Ultrasound (absence of steatosis only) ○ The Enhanced Liver Fibrosis (ELF) score ○ Transient elastography

	○ NAFLD fibrosis score • Quality of life (for example CLDQ, EQ-5D) • Serious adverse events
Importance to patients or the population	Establishing whether favourable changes in the gut microbiota improve NAFLD is of critical importance to a very large number of people in the general population and is also very important to a large number of people with type 2 diabetes or obesity who also have NAFLD. The prevalent belief that simple steatosis is harmless in NAFLD, is now being challenged. Increasing evidence is beginning to show that contrary to our previous understanding of the pathogenesis of disease progression in NAFLD, there is actually a significant risk of developing substantial liver fibrosis over time in patients who have simple steatosis, confirmed on initial liver biopsy.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the use of probiotics, prebiotics or synbiotics as primary prevention in people with NAFLD at high risk of chronic progressive liver disease and also at high risk of hepatocellular carcinoma.
Relevance to the NHS	With an epidemic of obesity across the developed world, the liver consequences of NAFLD (liver failure or liver cancer) have resulted in NAFLD becoming the second most frequent indication for liver transplantation behind hepatitis C. Since there are now effective treatments for hepatitis C, it will not be long before NAFLD is the most important indication for liver transplantation in the developed world. Unlike most other chronic liver diseases, NAFLD also causes problems beyond the liver. The presence of NAFLD in a patient with type 2 diabetes can make it very difficult to obtain good glycaemic control. NAFLD is also an important cardiovascular risk factor. Many general practitioners are also struggling with knowing how to manage patients with obesity and abnormal liver function tests due to NAFLD. Thus NAFLD has an important impact on NHS practitioners and services far beyond hepatology clinics. Since there are no licensed treatments for NAFLD, it is very difficult to help these patients who often struggle also with extreme fatigue because of their liver condition. Developing a safe, inexpensive, well-tolerated treatment to ameliorate, or even cure NAFLD, would have a marked impact on these patients' wellbeing and would lessen the burden on very many NHS services (attended by these patients).
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework.
Current evidence base	The current evidence is considered in Chapter 11 of the full guideline. Three RCTs identified assessed probiotics in adults and 2 in children. Modest improvements were indicated in terms of minimising progression of NAFLD in adults, but there was no evidence for this in children. All studies were of small sample size and variable quality. No evidence was identified on prebiotics. The limited evidence base does suggest promising results for treatment of NAFLD, but at present is not sufficient to base a recommendation on.
Equality	NAFLD increases with age and is slightly more common in men. The study design should recognise this and take account for age strata and both sexes in the randomisation process.
Study design	A randomised double-blind placebo-controlled trial is required to address this question. Patients with NAFLD would be recruited from secondary care where most people with NAFLD are diagnosed currently. Subgroups should include people with NAFLD and diabetes. People with simple steatosis or NASH should be included and patients with NAFLD and cirrhosis or NAFLD and hepatocellular carcinoma should be excluded. **Example intervention** Synbiotic:

	Probiotic: *Bifidobacterium animalis* subsp. *lactis* BB-12 at a minimum of 10 billion CFU/day (1 capsule a day). Prebiotic: fructo-oligosachharide with a degree of polymerization <10 at 4 g twice a day (2 sachets a day). Placebo: maltodextrin 4 g twice a day. Duration of intervention: at least 12 months for changes in liver fat; at least 18 months for changes in NAS score. Outcomes: improvements in NAFLD (that is, steatosis) as measured by MRI or MRS and NAS score by liver biopsy (see below other comments for discussion about the relative merits of assessment of liver histology. Improvements in glycaemic control HbA1c; insulin resistance (HOMA-IR); body composition (for example, by Dual Emission X-Ray Absorptiometry). Improvements: in gut microbiota measured in stool samples. For example, assess a change in gut (faecal) microbiota composition using • the 16S ribosomal RNA gene sequence-based method (16S rRNA) • fluorescent in-situ hybridisation (FISH) analysis, and • quantitative polymerase chain reaction (PCR). Further transcriptome, metabolome and proteomic studies are needed to determine the changes in the microbial metabolic activity with different dietary intakes. Understanding which dietary factor(s) affect which gut microbiota, and how they do so, and identifying which component(s) of microbial metabolic activity influence the host's metabolism, and how the gut microbiota contribute to NAFLD may help to develop new treatments for NAFLD. Ideally, new treatments for NAFLD should not only benefit the liver, but also have a favourable impact on the risk of other NAFLD-related comorbidities (such as cardiovascular disease and type 2 diabetes).
Feasibility	This study would be very feasible to undertake. NAFLD is highly prevalent and patients can be recruited from secondary care clinics where a diagnosis of NAFLD has been established and other causes of liver disease excluded. There should be no particular ethical problems, but patients consuming multiple courses of broad-spectrum antibiotics during the trial will need to be excluded and this could lead to a moderate drop-out rate during the trial.
Other comments	The trial may attract commercial sponsors. However, given the size of the problem, the potential impact to patients and the NHS, and the favourable policy context, a high quality study addressing this question would be an appropriate target for NIHR funding. One issue that needs to be considered is how to test the efficacy of the intervention: by non-invasive imaging of liver fat using techniques such as magnetic resonance imaging or magnetic resonance spectroscopy; or by assessment of improvements in NASH assessed on histological assessment of the liver obtained with a liver biopsy. To date, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require the demonstration of improvements of liver histological end points for the market approval of any new pharmacological compound as a treatment for NAFLD. Thus, an emphasis has been placed on improvements in liver tissue histology for proving efficacy of new treatments for NAFLD. Specifically, it has been believed that any new treatment for NAFLD should focus on improving non-alcoholic steatohepatitis (NASH) and should improve the histologically-derived NAFLD Activity Score (NAS) by 2 points with no deterioration in liver fibrosis. The NAS score assigns a maximum of 3 points for steatosis, 2 for ballooning of hepatocytes, and 3 for inflammation. This histologically-based approach to proving efficacy of a potential treatment for NAFLD has been predicated on the notion that improving histological markers of NASH is key to improving liver-related outcomes in NAFLD. The reason for this

	approach has been based on the interpretation of data from retrospective and prospective cohorts of patients who have undergone an initial liver biopsy, showing that only NASH patients with increasing stages of liver fibrosis are at risk of progression to end-stage liver disease. Implicit in this approach is the notion that assessment of liver histology is being used as a surrogate for a clinically-relevant liver disease-related end point. Such an approach has diminished a focus on finding treatments that decrease liver fat content itself as an early marker of disease, and thereby diminished attention on treating the liver condition in its early stages. Furthermore, since patients with NAFLD die two-fold more frequently due to cardiovascular disease than to liver disease itself, it is also important to ensure that any new treatments for NAFLD do not cause harm beyond the liver. In particular, it is crucial that new treatments for liver disease in NAFLD do not increase risk of cardiovascular disease or type 2 diabetes. For the majority of patients with NAFLD, early disease is characterised by development of excess liver lipid (containing intra-hepatic triglyceride) and liver triglyceride can be easily and accurately quantified by magnetic resonance-based imaging techniques. Indeed, the quantification of liver triglyceride with these imaging techniques correlates very well with steatosis identified by histology. In addition, these imaging techniques are more sensitive than the histology-determined steatosis grade in quantifying increases or decreases in the liver fat content and also provide better results than histology when steatosis has not involved the liver in a uniform manner. Improving intra-hepatic triglyceride content assessed non-invasively by either the magnetic resonance spectroscopy-proton density fat fraction, or the magnetic resonance imaging-proton density fat fraction, allows a focus on the early stages of disease in NAFLD. Such an approach has been used recently by several investigators, and the use of magnetic resonance-based techniques would also improve retention of participants within clinical trials. Many patients recruited to clinical trials testing interventions in NAFLD, are reluctant to undergo potentially painful, risky liver biopsies. Use of magnetic resonance-based imaging technologies in large prospective studies would help also answer the question of whether we can improve the stratification of type 2 diabetes or CVD risk in NAFLD, in order to therapeutically target the at risk individuals. A change of approach to using magnetic resonance-based approaches to testing primary outcomes in therapeutic trials for NAFLD, would also save a considerable amount of money (approximately £700 for biopsy compared to £300 for magnetic resonance spectroscopyin the UK at the present time). Since improvements in NASH can only be quantified by liver histology, it is also difficult to assess patients during follow-up with repeat liver biopsies, negating the utility of the technique outside clinical trials.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.4 Alcohol advice

Research question: Should people with NAFLD restrict their consumption of alcohol to below national limits?

Why this is important: In people with NAFLD, but without advanced liver fibrosis, there is uncertainty about the effect of drinking alcohol below national limits on progression of NAFLD. Some studies have suggested that modest consumption of alcohol (1 unit/day) may confer cardiovascular benefits and reduce likelihood of NAFLD. However there is concern that these studies have not accounted for other factors and that even modest alcohol consumption may accelerate progression of liver fibrosis in the setting of NAFLD. Ensuring people with NAFLD are given the correct advice on

alcohol consumption will reduce progression of liver disease and therefore reduce morbidity and cost to the NHS.

Criteria for selecting high-priority research recommendations

PICO question	**Population:** People with NAFLD, but without advanced liver fibrosis. **Prognostic variables:** Moderate alcohol consumption (from none up to the national limit) **Confounding factors:** Age, diabetes, BMI and gender. **Outcome:** Progression of NAFLD.
Importance to patients or the population	There are epidemiological studies reporting that modest consumption of alcohol (1 unit/day) may confer cardiovascular benefits and reduce likelihood of NAFLD. There is uncertainty though about possible confounding in these studies and concern that even modest alcohol consumption may accelerate progression of liver fibrosis in the setting of NAFLD. New guidance from prospective studies would reduce the likelihood of progression in liver fibrosis in patients with NAFLD. This would reduce progression to end-stage liver disease and reduce mortality.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the impact of consuming alcohol within national limits for people with NAFLD.
Relevance to the NHS	This would potentially reduce the burden of advanced liver disease and thus reduce utilisation of NHS resources.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework.
Current evidence base	The current evidence is considered in Chapter 14 of the full guideline. The current evidence base consists of epidemiological studies and thus may not adequately account for confounding factors.
Equality	There are no equality issues.
Study design	Patients with NASH and possibly some degree of fibrosis could be randomised to one of 2–3 arms of a clinical trial. In each arm they would be given advice to be abstinent, drink modestly (1 unit/day) or drink within recommended limits for the general population (14 and 21 units/week for women and men respectively). It may be worth considering patients who are not currently eligible for clinical trials of new pharmacological agents by not requiring a recent liver biopsy and using non-invasive assessments of liver fibrosis. A record of alcohol and dietary consumption in the groups should be undertaken periodically. Change in liver fibrosis would be a reasonable end point, which would require a 2–4 year study and approximately 200–300 patients. A hypothesis would be that abstinence or modest consumption was associated with a reduction in liver fibrosis compared to higher levels of consumption.
Feasibility	This trial would compete with ongoing and prospective trials of pharmacological agents and may be deemed less attractive for patients. An option would be to consider patients with NAFLD without a recent liver biopsy using a non-invasive marker for fibrosis as the inclusion criterion and outcome measure.
Other comments	The trial is most unlikely to attract commercial sponsors. However, given the size of the problem, the potential impact to patients and the NHS, and the favourable policy context, a high quality study addressing this question might be an appropriate target for NIHR funding.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.5 Pharmacological therapy for advanced liver fibrosis in children and young people

Research question: What is the clinical and cost-effectiveness of pharmacological therapy in children and young people with advanced liver fibrosis?

Why this is important: Observational studies reported that up to 10% of children and young people diagnosed with NAFLD progress to advanced liver fibrosis and will be at risk of developing advanced stages of liver disease. Pharmacological treatment (for example, pioglitazone or vitamin E) could prevent progression to advanced liver fibrosis or end-stage liver disease as has been reported in a number of high quality studies in adults with confirmed NAFLD. There are insufficient data on the efficacy of similar pharmacological treatment in children and young people with NAFLD to make clear treatment recommendations.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Children and young people with confirmed NAFLD and evidence of advanced fibrosis **Intervention:** Pharmacological treatment (for example, metformin, vitamin E, pioglitazone) **Comparison:** Placebo **Outcome:** Progression or regression of NAFLD severity as assessed by liver biopsy, ultrasound, transient elastography (with or without MRI or MRS, non-invasive markers of fibrosis); quality of life; serious adverse events
Importance to patients or the population	Identifying an effective pharmacological treatment option would prevent development of advanced liver disease in children and young people with confirmed NAFLD.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the use of pharmacological treatment in children and young people with NAFLD and advanced fibrosis and would therefore inform recommendations in updates of this guidance.
Relevance to the NHS	With increasing obesity rates in children and young people the prevalence of NAFLD and associated liver and non-liver complications will continue to increase, leading to a huge burden on many NHS services. Safe and effective pharmacological treatment (alongside lifestyle interventions) to halt progression of NAFLD and prevent development of advanced stages of liver disease would have a marked impact on patients' wellbeing and would lessen the burden on NHS services.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework.
Current evidence base	The current evidence is considered in Chapter 17 of the full guideline. At present, for children and young people with NAFLD, only limited data are available on the efficacy of pharmacological treatment, insufficient for NICE to make a strong recommendation for children and young people.
Equality	There are no equality issues.
Study design	A randomised double-blind placebo-controlled trial is required to address this question. In order to recruit sufficient number of patients and as liver biopsy in children and young people is only carried out in the 3 national paediatric liver centres, this should be a multicentre study involving all 3 centres. The study protocol should be designed to include assessment of progression or regression of NAFLD severity (as assessed by liver biopsy, ultrasound, transient elastography (with or without MRI or MRS, non-invasive markers of fibrosis)), quality of life and serious adverse events.

Feasibility	This study should be feasible to undertake although the number of patients with established fibrosis is likely to be small. Patients can be recruited across the 3 centres during the first year, but, in order to allow monitoring for efficacy, will need at least an 18–24 months follow up period (3–5 year study duration). Because of its potential risk there may be ethical issues in relation to carrying out liver biopsies at start and end of follow-up period.
Other comments	The study may attract commercial sponsorship from the pharmaceutical industry.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.6 Other research recommendations

1. What are the prognostic factors for the development of NAFLD or NASH in children and young people?
2. Is NAFLD a risk factor for the development of colorectal cancer?
3. How often should children and young people with NAFLD or NASH be monitored to determine risk of disease progression?
4. What is the clinical and cost-effectiveness of caffeine from coffee as an anti-fibrotic agent in adults with NAFLD?
5. What is the clinical and cost-effectiveness of pentoxifylline in the management of people with NAFLD?

Appendix Q: NICE project team

Name	Role
Sarah Willett	Guideline Lead
Martin Allaby	Clinical Advisor
Steven Barnes	Technical Lead
Ross Maconachie	Health Economist
Louise Shires	Guideline Commissioning Manager (until December 2015)
Ben Doak	Guideline Commissioning Manager (from December 2015)
Jill Peacock	Guideline Coordinator
Jaimella Espley	Editor

Appendix R: References

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